IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 13-CV-4507(CCC)

IN RE: DEPOMED PATENT LITIGATION

TRANSCRIPT OF
PROCEEDINGS

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Newark, New Jersey
March 17, 2016

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,
United States District Judge

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

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W I T N E S S E S

THE COURT: Let's get started. We're here on In re: Depomed. Let's just get counsel's appearances on the record and then we can resume with the witness.

(All attorneys are present)

THE COURT: Let us resume with the testimony. It's the direct of Professor Martin.

Professor Martin, you may approach the stand and I remind you you are under oath and that your testimony will continue.

MR.FITZPATRICK: Just before we start the testimony, if we could note for the record, as I indicated before we went on the record, that defendants will not be calling Dr. Hollingsworth to testify in view of the fact that his testimony will parallel Dr. Steed's testimony. And Dr. Steed was offered on behalf of all defendants. So we won't be calling Dr. Hollingsworth.

THE COURT: That is fine. Thank you.

S T E P H E N M A R T I N, sworn and testifies as follows:

DIRECT EXAMINATION BY MR. CAPUANO:

MR. CAPUANO: May I proceed?

THE COURT: Yes.

MR. CAPUANO: Good morning, your Honor.

THE COURT: Good morning.

Q. Just to reorient ourselves to where we left off yesterday, we went through the three stages for how a person of

ordinary skill in the art would go about designing a new analgesic in the early 1990s.

You testified, Professor Martin, do you remember, about what's shown here on the slide, the three stages first being selecting a lead compound by studying the prior art and selecting a lead, identifying the pharmacophore of the lead to determine what should be maintained, and what options were available for modification by studying the prior art structured activity relationships.

And then based on that modifying the lead according to the teachings of the prior art to make changes to structure and evaluate biological activities of the new compounds that were prepared.

Do you remember that testimony?

A. I do.

Q. Okay.

A. Is this on?

THE COURT: Tap just the top. Let's see.

THE WITNESS: May I get a pointer? I am likely to need one. Thank you.

Q. Okay. And having gone through those three stages like you did, you ended up here where you identified SS O desmethyltramadol as the most promising lead from the mixture of Tramadol and O desmethyltramadol isomers.

And you explained how the prior art motivated the

person of ordinary skill in the art to modify the OH group on the bridge carbon to hydrogen and open the ring to make compounds like linear compounds in Nazarov 1 that had central service system activity. And by doing so with those two changes a person of ordinary skill in the art would have arrived at Tramadol.

Is that a fair summary of what happened yesterday, Dr. Martin?

A. Yes, it is.

Q. Dr. Martin, I'm sorry, and result in Tapentadol. I said Tramadol.

A. Okay. Yes, Tapentadol as written up there in the slide.

Q. Thank you. And then we started to get into what Dr. Buschmann had testified about. And I will just start there.

You read Dr. Buschmann's testimony from his time in Court last week?

A. I did.

Q. Okay. And did you read where he testified about how the psychlohexane ring was necessary in Tramadol and O desmethyltramadol to obtain the correct positioning of the groups in Tramadol and O desmethyltramadol, the relative position of those groups?

Do you remember that testimony?

A. He said it was important. I don't remember the word

"necessary" necessarily, but certainly he acknowledged its importance.

Q. Would a person of ordinary skill in the art have believed in 1994 that the only way to get those groups to adopt that preferred orientation was by maintaining them as substituents on a closed cyclohexane ring?

A. No.

Q. And you've prepared a slide showing that preferred orientation.

What are you showing here?

A. Okay. So, I'm showing these Newman projections that we talked about yesterday. And we sort of introduced what they were. Because these are, these are at least one way of looking at these kinds of molecules that kind of simplify things in some ways and enable you to analyze confirmational issues which will relate to relative stability of different confirmations and thinking about what is the preferred confirmation and solution.

And so if we go over here to the cyclohexane derivative, you will see the orientations of these groups. And I didn't mention this yesterday but we call these equatorial. It's on this cyclohexane ring. And they are in the more stable orientation in this configuration on this cyclohexane ring.

And then the question is okay, so, can you have an acyclic molecule that still enforces that preferred

confirmation. And the answer is yes, definitely yes. And I tried to illustrate that here by considering this ring open compound and then looking at the Newman projection for this in exactly the same way I'm viewing the Newman projection for this.

So, essentially to just revise, review, we sort of imagine sitting over here and look at this carbon bond.

Q. Do you want to do it there?

A. No, let's just say here. And this is what we see. We can run through that stuff again. But, this is what we see. And what we see is almost exactly what we see over here. We see the relationships of this group with the nitrogen and the two metals and its relation to the AR.

What I didn't say yesterday is this AR is a shorthand notation for this group up here. AR means aryl. And so it's, without cluttering the drawing, it's easier to draw that way.

And the important thing to note again is in this confirmation here, these groups, the aryl group and this group are oriented in space exactly the same as they oriented over here. If you look at all the other atoms that are present in both molecules, this atom here corresponds to that atom over there. This little atom here corresponds to this atom here. And then this atom here is this circle in the back.

So, fundamentally what this is telling us is that this acyclic molecule has the same preferred confirmation in

solution, let's say, as the cyclohexane, the arrangement, as I said, with the pharmacophore. The important thing is how these things are arranged. They are arranged the same way.

Q. And when you say acyclic, is that another way of saying open chain or linear, that terminology you've been using?

A. Yes. Acyclic, linear, open chain are all equivalent terms.

Q. And then we learned about Newman projections. We got out our models and we went through these slides showing the two adjacent carbon atoms. We turned it around as shown on the animation to look at our models with the yellow, blue, red and white substituents and we explained how that is the same as what you'd see in a Newman projection.

And we had a little tutorial about Newman projections. Is that fair?

A. Yes, I think so. I hope it was informative.

Q. Okay. And then this, in fact, is where we left off when we stopped yesterday afternoon.

Professor Martin, can you explain how using this slide, slide Number 49, how using Newman projections a person of ordinary skill in the art can determine which are the preferred orientations and whether those preferred orientations are the same as what you would have in Tramadol?

A. Okay. So right so we kind of got started on this. And so this Newman projection is a replication of what we saw

previously with some additional notes. And that is these little red double headed arrows which I referred to as a Gauche, Gauche, people pronounce this differently, interaction and these are unfavorable.

Basically they represent steric interactions, repulsive interactions between atoms on this here which was originally the blue ball. I wish I had labeled these blue, red and so forth as well, but I didn't.

But this would be the blue and this of course is the red. And then there's this interaction over here which is similarly unfavorable again a Gauche interaction.

Q. Why are these unfavorable?

A. Because of the steric repulsion. And so at the very end I modified my model slightly and I modified your Honor's model. I didn't modify your model. I am happy to do so if you wish. It's just these little plastics things that sort of designate that the substituents you know this nitrogen here and this aryl group are bigger than the other ones.

MR. BEST: I think we remember enough chemistry to follow.

A. All right. Thank you. I did modify it because it is important. So again if we take that same perspective and if you view down this bond, if you view down this bond, you see these bigger groups are together. And if you just kind of rotate these plastic things, you can see how they bump into

each other.

And so these plastic things actually are a better representation of the space that these atoms occupy. These little balls aren't really don't represent this actual spatial requirement of these groups. And so the bigger, you know, the bigger the ball, you know.

THE COURT: So, is the repulsion just caused by size or are there additional elements to that?

THE WITNESS: You know, if we leave it at size, this is easy. We can see electronic repulsions and things like that. But it's basically the size they are physically bumping into each other. And so that causes, what that does is it increases the energy of that particular form.

And so if we accept, for the moment, and its inarguable, I think, that these Gauche interactions are bad, then all we have to do is look at the various different confirmations I've presented here.

And what I've done here is presented the three more stable confirmers that we have here. And I can go into detail if you wish. But I think let's keep it simple and just look at these. And if we just count these Gauche interactions, so wherever this angle here is 60 degrees. And anytime you see two groups with that angular relationship, that's bad.

And so if you can imagine and if you take your model and you rotate 120 degrees, you get a different

presentation that has the blue, the blue ball down.

So remember the blue is this nitrogen. So if you kind of keep that, that's a reference point. I'm just rotating this front atom. So then the blue goes down and you see that the blue is still interacting with this red. So that's bad. But if you count these Gauche interactions now, there are 3, one this interaction here, two, this interaction here, and three, this interaction here.

And then if you take the step again and you hold the model and you rotate by another 120 degrees, you get that. And now you see the red ball and the blue ball are away from each other. So that's actually a bit better. But, you still have, if you count them, and again you can look down the model and you can count them too, you can see that there's an interaction here between the blue and the white, between the white and the yellow, and between the yellow and the red.

Do you see that?

THE COURT: I do.

THE WITNESS: Okay. And so that's bad too. So that's this picture over here. There are three of these interactions.

And so the more of these interactions you have, and of course the size of the groups matters too, but to keep it simple, we can just count these interactions. And so this confirmer, confirmer A I've labeled here, has only two of

these interactions. Confirmer B has three. And confirmer C has three as well.

And so what that tells the sophomore in organic chemistry at least at the first pass is that this confirmer is the more stable, most stable of these three confirmers and it is this confirmer, remember, that corresponds to the way the atoms were arranged on this cyclohexane ring.

And so I think yeah, thank you, so this is the same thing as confirmer A. And this is the representation of, in this particular case, this molecule here which was not Tapentadol, by the way. And if we look at the representation of the cyclohexane ring, it's the same.

So, this acyclic form is the more stable form of this molecule. And the more stable form of this molecule corresponds to the more stable form of that molecule.

And so that would tell one of skill in the art that this particular molecule, this one here, would adopt a three dimensional shape with respect to the important parts in terms of biology. It would maintain the same spatial relationships that this molecule here had.

And I think this is really important because it is important, we touched on this a little bit yesterday, but when you think about how you're going to open the ring, as I mentioned, there are many ways. And we will get to that I think later. And there are many ways you could do it.

But, whatever ways you would pick to do it, you would maintain these stereocenters and the substitution at these stereocenters because that's the only way that you can maintain the relationship in this acyclic form that you need to have that corresponds to the cyclic form.

Q. Thank you, Professor Martin.

MR. CAPUANO: For the record, Professor Martin is pointing to demonstrative Exhibit 48.

Q. Professor Martin, you also brought some bigger models with you, according to the plaintiffs.

Can you use those bigger models to show how in the linear open chain configuration of Tapentadol that it adopts or can adopt in its lowest energy form the same orientation of the groups as in the cyclohexane version like Tramadol?

A. Sure. So what I did throughout my testimony is exemplify things from the RR series, from the RR Tramadol, RR desmethyltramadol. And the reason for that is that's how I exemplified things throughout my expert report and everything. So I wanted to keep that consistent. But, the models I've made are different.

So, I mentioned a moment ago that this molecule here with R equals H is not Tapentadol. It's the enantiomer of Tapentadol. And the models I've created and have distributed to the Court are models actually of Tapentadol. So that's the mirror image isomers of these two molecules here. So they

are --

Q. Have you done everything with the RR on the slides?

A. Yes.

Q. Does that apply equally to the SS?

A. Oh, yes, yes because they are enantiomers. And I think it's been established in Court that enantiomers have the same physical properties except with respect to the way they rotate the plain and polarized light.

They also have different properties when they interact with chiral environments. But, as far as these molecules and solution, they have the same energetics. So they are identical essentially.

Q. In terms of presentation, is it the case that you used RS, RR just as simplification or to be consistent and there's no difference between what's going on in RR and what would be going with SS?

A. Not in terms of this analysis, no. They are identical.

Q. Okay.

A. So this I don't know how much people have played with their models and we will see in a minute. But, if you pick the model up that has this cyclohexane ring, this closed ring, and you orient it so this six membered ring here, this flat is up on top and this side chain here with the blue atom at the end is on the left.

And then you take the molecule that actually has a

broken ring which corresponds to the molecule up there on the right, except the mirror image you can sort of lay them right down on top of each other and you can lineup the aromatic ring and you can play around with this a little bit and lineup the rest of the molecule. So it's exactly the same. Have you been able to do that?

THE COURT: Let me play around with it a little bit.

THE WITNESS: There it is. And you can see that they superimpose on each other. And all those important atoms are arranged in the same places. And you can actually move them around a little bit.

A. So I mean if you wish you can twist, let me just pick one of them because there are some flexibility, there are some points of flexibility here. You can turn this.

I put sort of restricters on this big ring up here. But, you can turn it and you can turn equally in both of those compounds. So, you know, these molecules are going to adopt, they are going to change their confirmation from what we are seeing here when they bind.

But the important thing is whatever rotations you do with this big ring on the top or this thing with the blue on the end, however you want to do that, you can do it on both molecules. And then you can sit them down and superimpose them again.

So I think that's why it's good to leave them with you and you can play with them and you can actually convince yourself that yes, they sit right on top of each other.

Now there's one other difference that I need to alert you to. On the molecule that has the six membered ring, you see that it's got this little red thing, extra thing there. Do you see that? Hopefully it hasn't fallen off.

THE COURT: Which one is that?

THE WITNESS: That little red right there. Exactly. That's extra. And that is the hydroxyl group on O desmethyltramadol.

Q. Is that the aliphatic hydroxyl group?

A. Yes, that's that bridge hydroxyl group. So the two molecules that we are comparing here, actually can you go, we had the slide where we went through the analysis of how we get to Tapentadol from O desmethyltramadol.

A. Right. This one. So the molecules you have in your hand are this one and this one. And so you see this little red box here. That's that little red atom. That's an oxygen. And that thing at the end of it is the hydrogen.

So at the end of all of these, wherever you see this painted thing, at the end of that is hydrogen atom.

THE COURT: Okay.

A. So, the models then correspond now to this structure and this structure here. And as I said, you know, these can

adjust and will adjust. And I've drawn these things in a particular orientation. But you understand that there can be flexibility.

THE COURT: Okay. And just so I'm clear, the difference between the red and the blue is what?

THE WITNESS: The red is oxygen and the blue is nitrogen.

THE COURT: Thank you.

THE WITNESS: Yes, you're welcome.

MR. CAPUANO: And just for the record also, Professor Martin is pointing to slide Number 43 in his testimony just now.

Q. Professor Martin, do you remember that you see when looking at options to open the cyclohexane ring, one of the options that you listed as possible was the option of what you called scission. And I'm looking at slide 50.

And you pointed out that you could open the ring by cutting or in designing a new molecule that could be envisioned by cutting bonds at either A, B or C? Do you remember that?

A. I did.

Q. You said you would come back and explain why, although that was a possibility, it wouldn't have been a preferred way of going about it.

And using slide 50, can you explain for the Court why a person of skill in the art would not have found scission, the

scission option of opening the ring to be a promising option for modifying the cyclohexane region of Tramadol and O desmethyltramadol?

A. I would like to revise it to as promising, not promising all together. But, there are two references here. First and foremost is the simple one. This gets really complicated. But, the simple answer that I think would have directed one of ordinary skill is when they consulted the prior art and looked in the literature for compounds like this one, like this one, or like this one, I don't have identifiers for these.

This molecule results from scission A. This molecule results from scission B. And this one results from scission, am I --

Q. I just wanted to point out where you were pointing on slide 50. That's all. Just to be clear.

THE COURT: You know what, I think it's a good idea to just keep doing it with each reference so we can at least go back and look at it.

So when we did A just now scission A I guess was in the middle of the slide at slide 50. It is the third figure on the right. Scission B I think was on bottom side on the left. And C was on the right side on the bottom as well.

THE WITNESS: Right.

MR. CAPUANO: Thank you, your Honor.

Q. Professor Martin, you and I both --

THE COURT: I know it's hard to do but it would make for a more complete transcript.

THE WITNESS: I forget about having records that you all can look back on afterwards.

THE COURT: Thank you.

A. So let me try this again. So, there are these three scission possibilities. So if you look at the top structure here on the slide 50, as you showed, there are three possibilities I considered. And you asked maybe why you didn't consider cleaving other bonds in this figure.

And the answer to that question is simple. The answer to that question is that when you cleave other bonds, and I don't need to identify what they are other than A, B and C, you will no longer have the stereocenters that are critical to maintaining confirmational control.

So, you no longer have the stereocenter as what Flick referred to as the bridge carbon atom. And you no longer have this stereocenter to carbon aminomethyl side chain, okay.

So, again, these compounds, as far as I could tell, are not precedent in the prior art. So that's one thing. But, the other thing which gets more complicated is to look at this one, this is scission A. So this is in the second line of the slide. And going across, you can imagine cleaving this bond and then this molecule in the center here would be the

resultant molecule where we'd now have two of these methyl groups, these CHC groups in the middle.

And the problem with doing that is that these groups now are really bumping into each other. They are really close. And you can get a sense of that if you go back and look at the model and if you, you can actually pull this apart. It's a little hard. They pop.

Q. Do you want the Judge to pull those apart?

THE COURT: I'm not going to pull mine apart because just because I like it intact. I will watch yours.

THE WITNESS: You may not get it back together. So, I've just pulled it apart. But, if that's all I do, these atoms are right next to each other. Remember I told you that bumping into each other is bad when we look at the Newman projections. So, this is terrible.

I mean these two atoms are within distance where they want to be bonded and connected to each other but they are no longer connected. So, they are very unhappy and now get out of the way. And all of a sudden we've got something. But, whatever that is would maintain confirmational preferences here.

But the problem is is that we are not going to maintain relationships of these two carbon atoms, let's say for example as we had over here. This side chain is now going to do all kinds of things.

Q. You're pointing to the center?

A. Sorry, the central carbon. This side chair will do all sorts of things to get rid of these interactions. And one example of that's on the third drawing in the second line, that's one possibility.

But the point here is now if you think about where the atoms are, you have less control here.

Q. Professor Martin, when you do the scission at bond B or bond C, do you end up with that same --

A. You have the same problem.

Q. -- bad bumping into relationship that you showed for scission of bond A?

A. Right. And so in that case the point is is that the atoms that remain, that you have remaining in this structure, once you cleave the bond, the atoms that remain cannot adopt the same positions in space as they did in the starting material. They have to change dramatically.

And so I would say that's less preferred. It's certainly not something one couldn't do. One might do it but it would be something that would be secondary, I think, to the other analysis. And so yeah -- okay, never mind.

Q. And so one of the other options that you said was available for opening the ring was excision.

Do you remember that?

A. I do.

Q. And you showed us how by excising what you've labeled here on slide 51 with the blue circle one how excising that guided by Nazarov one prior art would lead to doing that with SS O desmethyltramadol would lead to Tapentadol.

But you also said one option would be excising carbon atom labeled two or even excising both carbon atoms one and two. And can you explain for the Court why it is that a person of ordinary skill in the art would not be motivated to excise carbon two or carbons one and two over the preference for excising carbon one again?

A. Again I would like to characterize it as less motivated. Again I am looking at preferences of what one with ordinary skill in the art would do and the priorities that they would set forth based on prior art teachings. And I think it's important to keep that in mind.

I don't want to take the position that these are not possible or even maybe as good. I'm taking the position that they are not guided by prior art. They are guided more by thoughtful analysis.

And so the box we have in red with Nazarov there again I picked that one because of its prior art precedent. It's not just Nazarov, by the way, it's also Spasoff (ph) which didn't get on this slide but I think we talked about it.

So, this on the third line here these two compounds on on the third line are enantiomers again.

Q. We are again talking about slide 51?

A. Yeah. We are still on slide 51. The third line. We're talking about enantiomers. And the third line represents the case where we would remove or excise carbon atom or methylene Number 2, okay. And these compounds would have the same confirmational preferences as this one.

Q. And this one is the one in the red box?

A. Sorry, the one in the red box. And then the last pair on the bottom, the fourth line, these compounds, this pair of compounds arises from removing both carbons one and two in the top line of the slide Number 51. I have to keep saying that, I guess.

So, these compounds too would have the same confirmational preferences I think largely certainly with respect to the pharmacophore as compounds in the red box. But, I pick the ones in the red box as being those guided by prior art. And so that was why we started with those because these, these are the ones explicitly I think precedented in the prior art.

Q. Now, Professor Martin, having arrived at the idea to make Tapentadol hydrochloride -- to make Tapentadol, would a person of ordinary skill in the art know how to actually go about synthesizing it?

A. Oh, yeah.

Q. Okay. And what would be involved in that synthesis?

Not specifically, but --

A. To make Tapentadol?

Q. Yes, sir.

A. Well, I mean there are many references in the literature to making compounds like this. We have Nazarov, for example, in 1955 who sets forth a very simple way of making these kinds of compounds. And so Spasoff years later. I mean it would be a very simple thing to make Tapentadol.

Q. Are you aware of any of plaintiffs' experts who have testified that it would be other than routine to make Tapentadol once having decided to make it?

A. I'm sorry, are you saying do they think it would be difficult to make?

Q. That's another way of saying it, yes.

A. I am aware of no testimony that says it would be difficult to make.

Q. Okay. And in making Tapentadol and thinking about salt forms of Tapentadol, would a person of ordinary skill in the art be motivated to make the hydrochloride salt of Tapentadol?

A. Well, sure. I mean we're starting with Tramadol and Tramadol was marketed as a hydrochloride salt. So, I mean the analogy comes straight through from Tramadol to where we are now.

Q. Okay. Can I have defendant's Exhibit 176?

Professor Martin, do you recognize defendant's

Exhibit 176?

A. Yes, I do. It's a paper by Steven, I'm not sure how he pronounces his name, Bergee published in 1977. And essentially it's a review article on pharmaceutical salt forms.

Q. Can we have Table 1, the top of the next page?

What's presented in Table 1 of this defendant's Exhibit 176?

A. Well, I think if you look at the title of the table it tells you, it says that Table 1 is a table of the FDA-approved commercially marketed salts as of 19, well, the date here would be 1977, right. And so we have quite a few. I don't know how many, forty plus. I don't know what the exact number is but quite a few.

Q. And these are approved salts and the percentage of approved commercially marketed salts, and it goes through starting with acetate and on down. Is that right?

A. It does.

Q. And for example acetate 1.26. This one benzenesulfonate 0.25.

Do you see that?

A. Yes, I do.

Q. What's the percentage for hydrochloride salt?

A. Hydrochloride is almost 43 percent. So the vast, well, certainly the majority, vast majority I guess of plurality, I am not sure is the word, but the greatest fraction

of hydrochloride salts, I guess the next closest one, I don't know, is well a chloride and bromide. So I am not sure what the difference is.

Q. Professor Martin, remember we talked about the claims of the '593 patent?

A. I do.

Q. And we looked at claims 8 and 17. And you testified that those were method claims.

Do you remember that?

A. You mean 117?

Q. I'm sorry, thank you. Claims 8 and 117.

A. Yes, I said they were obvious. And why did I think they were obvious?

Q. Thank you. That's a good question.

A. Sorry. I got hung up on correcting you.

Well, I think they are obvious. These are method of use claims that relate to using Tapentadol as an analgesic compound. And we've started with an analgesic compound Tramadol. And we've modified that compound with the intent of making an analgesic compound. So, it's pretty obvious to me that it would be an analgesic compound to treat pain.

Q. Okay. And Professor Martin, finally, have you prepared a slide that summarizes your opinions in this matter?

A. I have.

Q. Could you read that into the record, please?

A. So a POSITA in 1994 would have selected Tramadol O desmethyltramadol and their individual enantiomers as lead compounds for developing new analgesics. And I think we said that we would preferentially select the minus O desmethyltramadol of all of those.

The prior art in 1994 would have motivated a POSITA to modify the lead compounds to arrive to Tapentadol. The asserted claims of the '593 patent are invalid as obvious in view of the prior art as a whole which would have suggested to a POSITA to make Tapentadol with a reasonable expectation that it would be effective to treat pain.

Q. Thank you.

MR. CAPUANO: I have no further questions, your Honor, at this time.

THE COURT: Thank you. Let's turn to the cross.

MR. BEST: I believe we have some binders to hand out.

THE COURT: Let's take care of that. We will find out if there is any issue and then we can move forward.

Please, everyone, take a look at the exhibits and let me know if there is any issue.

MR. CAPUANO: We have no objection to the exhibits, your Honor.

THE COURT: Thank you. Let's proceed.

CROSS EXAMINATION BY MR. BEST:

Q. Good morning, Dr. Martin.

A. Good morning, Mr. Best.

Q. Now, could we start with PTX 54, the Nazarov reference to which you referred extensively this morning?

Now, you testified that this reference would have motivated a person of ordinary skill to remove a carbon atom from a structure like the Tramadol compounds to generate linear compounds.

Is that right?

A. That's correct.

THE COURT: You know, I'm sorry, we are just going to close this. I'm sorry. Go right ahead.

MR. BEST: No problem.

Q. Actually for a moment could we see Dr. Martin's direct demonstrative Number 51?

I believe you referred to this demonstrative in some of that testimony. Is that correct?

A. It is.

Q. You would agree with me that Nazarov only particularly describes one compound in terms of biological activity, correct?

A. That's my recollection. Well, he said one particular one has really strong activity.

Q. Yeah. Let's focus on that and perhaps it will help.

Could we have PTX 54 once more at Page 4?

Q. Can we highlight the last sentence of the second paragraph?

Is this the passage of the Nazarov reference to which you just referred?

A. Right. He says The most interesting substance turned out to be -- do you want me to read the rest?

Q. No, I think that's sufficient.

Now the chemical structure of this compound, and I believe --

THE COURT: What is your exhibit for this one?

MR. BEST: It's PTX 54. I think there's also a DTX number.

THE COURT: Is it?

MR. BEST: But I don't know.

THE COURT: Is it 729?

MR. BEST: 729.

THE COURT: Okay. I have it.

Q. I believe this substance is identified as compound 14 in this reference. Is that right?

A. Yes, it is.

Q. Okay. And I believe the chemical structure of compound 14 is referred to in this reference. Isn't that correct?

A. It is.

Q. And could we see that on the prior page, please? And

would you highlight that structure and the bit to the right of it?

And in this case compound 14 is referred to as having an R group of methyl and an R prime group of basically a phenoxy acetic group, correct?

A. That's correct.

Q. And I think that you noted yesterday this is a bit of an awkward structure. So we've redrawn it to make it a little clearer.

Could we have my demonstrative Number 4?

Now, on the right would you agree that this is the compound 14 that was described in Nazarov?

A. I believe that's accurate, yes.

Q. And as you can see on the left I have depicted the minus enantiomer of Tramadol the S S O rather it's metabolite, the S S O desmethyltramadol, correct?

A. Yes.

Q. Now, would you agree with me that the Nazarov compound has a phenyl ring attached to what we referred to throughout these proceeding as the bridge head carbon?

A. A phenyl ring, well, it's got more than a phenyl ring. It's got this entire ester. Is this what you are referring to.

Q. I'm not. I am referring to the phenyl ring attached to the bridge head carbon directly.

A. Right. So that's the same as what I had shown before

earlier.

Q. Now, so that Nazarov compound is not like Tramadol or as in this respect. Is that fair?

A. It differs in that respect only by this hydroxyl group. That's correct

Q. By hydroxyl group, you mean the hydroxyl group that would have attached meta to which that phenyl group is attached to the rest of the molecule, correct?

A. Correct. And in the desmethyltramadol structure, you have in the right that hydroxyl group is present whereas that hydroxyl group is not present on Nazarov. That's correct.

Q. And this compound was singled out for, I believe you called it its strong biological activity, right?

A. I said these compounds that had this linear framework that would be analogous to those compounds that would derive from taking, in this particular case O desmethyltramadol and removing that one carbon atom which I think we labeled as number 1.

I said I was referring to those atoms themselves. I wasn't referring to the entire pharmacophore of Nazarov. Nazarov doesn't have, clearly it doesn't have this hydroxyl group which we learned yesterday from Flick is so terribly important.

Q. So, thank you for that explanation. But, I was asking a pretty simple question.

You would agree with me that you described this compound, in fact, the paper describes this compound as having a strong biological activity, correct?

A. I did.

Q. So wouldn't you agree that Nazarov teaches a person of ordinary skill to employ a phenyl group of linearized compounds such as this depicted?

A. It shows that a phenyl group there is effective, yes.

Q. Now looking at the bridge head carbon once more, you see that the O H group here, which also appears in the O desmethyltramadol structure, the aliphatic O H has been esterified, correct?

A. I do.

Q. Now and in fact I think we discussed before, the Nazarov compound has a phenoxy acetyl group here, O desmethyltramadol. It's a free OH, correct?

A. That's correct.

Q. So again the Nazarov compound is unlike either Tramadol or its metabolites in this respect, correct?

A. Well, this particular Nazarov compound that you've drawn up there, yes. But the precursor of this Nazarov compound for which I don't have any specific information regarding its biological activity, I don't know whether those compounds were tested. Nazarov simply tells us that this was the most active compound.

The point is is that the precursor to this molecule has that O H on it. And that molecule very much more resembles the Tramadol structure on the left-hand side of this slide that you've represented.

Q. And just to confirm, you just said that you do not have data regarding the biological activity of the OH precursor of Nazarov compound 14, correct?

A. No, he didn't, he really called out this compound on the right as being the one that was most interesting. So, obviously others were interesting since this was most.

Q. Well, actually this is the only compound he calls out as having any particular activity, correct?

A. He said it was most interesting.

Q. Now, and wouldn't then this compound have taught a POSA to provide the phenoxy acetyl ester of a linearized compound such as Nazarov compound 14 rather than the free OH in developing a new analgesic?

A. So, well these were anesthetic acts. I think they are different from analgesics. I said these compounds DCNS activity.

I think what Nazarov teaches is that of the compounds he looked at and the esters he looked at, I guess, and again I don't know what else he looked at, he said this is the most promising.

And so I guess yes, if you're going to make that

compound, then he's teaching it looks like you should put an ester on this, yeah.

Q. Now, you just made a distinction, I believe, between anesthetic and analgesic activities. Is that right?

A. Right.

Q. And so is it fair to say that Nazarov only teaches a person of ordinary skill how to create potentially effective anesthetics rather than potentially effective analgesics?

A. No. He didn't test for analgesic activity so far as I know. He did teach about anesthetics. So he teaches the anesthetic part.

Q. So there's no data in Nazarov relating to analgesia, correct?

A. Correct.

Q. None of those compounds were tested for analgesia, correct?

A. I can't answer. I don't know.

Q. That's fair. But, the paper reports no compounds as having been tested for analgesia. Is that fair?

A. It doesn't say that they were not, yeah.

Q. Which means that, yes, it's correct that the paper does not indicate?

A. Okay. Sure. Sorry.

Q. No problem. In fact, if we look back at the paper, the Nazarov paper at Page 4 once again and focus in on that same

paragraph, the comparison that's made here between compound 14 is with a compound called dicaine, correct?

A. Yes.

Q. And dicaine is a local anesthetic, correct?

A. That's my recollection. It's been a long time since I looked at this particular reference. I looked the structure up but I have forgotten what it is.

Q. Now, is it fair to say or you agree with me that the Nazarov compound was synthesized a mixture of stereoisomers?

A. It looks like it's a mixture of four different compounds. I would guess there are two stereocenters that reaction is, I don't know that that reaction generated those stereocenters as particularly stereoselective.

So, yeah, I would anticipate a mixture of two different diastereomers and the enantiomers of both of them, so four compounds.

Q. And if I could have my structure again which I think is my demonstrative four.

Is it fair to indicate that sort of mixture of stereoisomers with only indicating straight lines rather than the dashed in solid wedges?

A. I don't know. You kind of have to be careful how you evaluate that. You don't know necessarily what people are trying to do when they represent things.

But, normally, if you look at a structure like that,

and of course when they drew the structures they didn't draw them like this, they drew a representation, I would say, that's analogous to this that didn't have any stereochemical descriptors. And so you would look at that and say yeah, it certainly could be four different compounds.

Q. And when you say that, you mean the structure I've drawn?

A. I'm sorry, yes, the structure from Nazarov on the right.

Q. Thank you. Now, the composition of -- and so Nazarov, you would agree, teaches a person of ordinary skill to employ a mixture of stereoisomers in developing a new analgesic using Nazarov as a basis?

A. Again right. So I mean what he teaches is that the mixture is active. I wouldn't say that he teaches that this is the best thing. He doesn't go any further than that. And I don't know what they did subsequent to this.

But, if they were truly interested in this, they would have separated the diastereomers. They would have tested each of the enantiomeric diastereomers and if they found activity, then they would have separated those enantiomers and tested them each individually is what they would have done. But, they didn't do that here. So we don't have any information. I wouldn't say that it teaches this is the thing to do. It says this works.

Q. But, at least it doesn't teach you that you need to separate those stereoisomers?

A. No, you don't need to separate them and you still get activity. So, that's a good thing.

Q. Nazarov was published in 1955. Is that right?

A. Yeah, he had several papers. This one is from A55.

Q. The Flick article you have spoken of at length I'm sure we will discuss was published in '78. Is that right?

A. That's correct.

Q. You would agree that Flick and his colleagues were not motivated to make linear compound on the basis of Nazarov since it was available in the art for more than 30 years, correct?

A. Well, I can't answer that question. They don't report making any such molecules. I don't know whether they considered it. I have no idea what they were thinking. They didn't report it. They weren't motivated to report on that in this paper. But, I don't know anything more.

Q. But the Nazarov compound was available in the art to them before they published the Flick paper in '78. Is that right?

A. Yes, it certainly was available. I don't know whether they looked for it.

Q. And they didn't make linear compounds as a part of the Flick study, correct?

A. That's correct.

Q. Now, you testified that you've read Dr. Buschmann's testimony rendered in this litigation last Thursday, correct?

A. Yeah, I read through it is how I characterize it. I hope I don't have to take a test on it.

Q. Fair enough. I think mostly the answer is no. But, you've answered a couple of questions on it so I'm going to ask you a couple of more.

You should then recall that by 1991 Grunenthal has synthesized at least more than 500 more compounds that were analogs of the Tramadol compounds, correct?

A. Yeah, I think at the end I remember a number upward or I remember the number 900 somewhere. I remember a number like 870 somewhere. But yeah a lot of compounds over the course of the project.

Q. And in all the time between, and again having read Dr. Buschmann's transcript, in all the time between 1978, let's say and 1991, none of the compounds that Grunenthal reported as having made with linear compounds, correct?

A. I believe that's correct. I reviewed I think Buschmann was the first. My understanding is Buschmann was the first to have done that. I looked at Dr. Buschmann's notebooks, at least some of them.

I'm sorry, could you ask the question again.

Q. Sure. Is it fair to say that, well, I think I'm not actually sure there was a question on the table. But, let me

ask you this, in the time going up to 1991, is it fair to say that the Grunenthal scientists were not motivated by Nazarov to make linear compounds, correct?

A. Well, I believe that's the case. Because I believe it's the case that Buschmann was the first.

As far as my understanding is Buschmann was the first. And in my looking at some of his notebooks, I recall the first of these being the earliest date I remember was '92. So that's what I know.

So from what I know maybe the answer to your question is yes. But, I don't have access to all the other things that they were doing.

Q. That's fair. You are aware of no evidence that is contradictory, however, correct?

A. I am aware of no evidence that's contradictory, no.

Q. Now could we look at the Spasoff article which you discussed briefly yesterday DTX 739? I am sure it's in defendant's binder but not in mine.

A. It's not in mine.

Q. Do you recall testifying about the Spasoff article yesterday?

A. Yes.

Q. Would you agree with me that no compounds discussed in Spasoff were analyzed for their analgesic activity?

A. I don't think so, no. They were, there's no data in

Spasoff. But, there is a comment in Spasoff where he says certain compounds had better -- did you say analgesic activity?

Q. I did?

A. Okay. Let me go, there's a sentence in here.

Q. Let's highlight what I'm pointing at. This may help you.

Are you thinking of this last sentence of this paragraph?

A. No, there is another sentence where he talks about the threo compound. And there's a reference to a footnote nine. Aramova, (ph) I think is the reference.

Q. Right.

A. I don't remember what they tested these compounds for. And again I did focus on CNS activity as being the guide here. I mean CNS is at least CNS and then you have a chance at analgesic if you are interacting with the nervous system. I could try to find the sentence if you want.

Q. Please do.

THE COURT: That's all the stuff from yesterday, right?

THE WITNESS: Right.

THE COURT: That's DTX 739.

Q. Let's try the second page of the PDF.

A. 729 you said?

THE COURT: I think it's 739.

Q. 739. Have you found it?

A. I think so. The beginning of the last paragraph.

Q. Yes, exactly. Now again because I'm not sure there was a clear question on the table right now, but you would agree with me that Spasoff does not discuss any of the compounds disclosed therein having been tested for analgesic activity?

A. He does not say that they were tested for analgesic activity. That's correct. He says they are tested for central nerve activity and things like that. I don't, I don't know exactly what it says.

Q. There's a focus on this reference Number 9, right?

A. I beg pardon.

Q. There's a focus in response to I think you are relying on this first sentence of the paragraph beginning the neuropharmacological screening. Is that right?

A. Yes, yes.

Q. And he refers to what he has called reference Number 9, correct?

A. That is correct.

Q. And if we look at reference Number 9 in the back, that points to Navramapo (ph) paper, correct?

A. That's correct. And that does exist somewhere.

Q. In fact, it exists in your binder from yesterday. If you look at DTX 851. If we could look at page --

A. DTX 851?

Q. 851. If we could look at the third page of that.
A. Are we going to use models or not?
Q. Maybe. You can set them aside for now.
A. Okay. I have the reference.
Q. Now, do you see any reference to a study of any of these compounds that were discussed in Spasoff relating to -- withdrawn.
Do you see any references here to a test of the Spasoff compounds for their analgesic activities?
A. I will have to read it. Where?
Q. Start with pharmacological study.
A. Okay. Okay. So they test them for toxicity and basically they tested them against reserpine. I'm not a pharmacologist. I don't know what that particular thing is. I don't know. It may be related to norepinephrine.
Because the epinephrine that they mention is, as I remember, is a norepinephrine reuptake compound. And we talked about the norepinephrine antinociceptive pathways yesterday. And they are doing some comparisons, it looks like, with epinephrine.
If you look at Figure 2, they are certainly, if one connects the norepinephrine analgesic pathway, you can say there's some information here. But, the tests per se were not for analgesia.
Q. In fact, they were for ptosis, p-t-o-s-i-s and

catalepsy and tremors. Isn't that right?

A. Yeah. Amongst the things for the reserpine beyond what the toxic effects, yeah.

Q. Now, Spasoff -- we can go to the front page. Actually Spasoff was published in 1981, correct? And I think --

A. I believe.

Q. It may be '77.

A. '77.

Q. Does that look correct?

A. '77, yes.

Q. So, this was available to Grunenthal scientists by 1991, correct?

A. It was.

Q. And Spasoff did not encourage any of them to make linear compounds. Is that right?

A. I can't answer question.

Q. Well, they didn't make any linear compounds as a consequence of reading Spasoff, did they?

A. Not to my knowledge. Well, although I don't know. Buschmann may have. I don't know what motivated, I don't know what exactly prior art he looked at.

Q. Do you have any evidence whatsoever that he looked at Spasoff at any point?

A. Dr. Buschmann?

Q. Correct.

A. I have no evidence, no.

Q. Now, you testified previously about how a POSA -- and, by the way, I have used the term a couple of times. If I use the word "POSA" will you recognize that to be person of ordinary skill in short?

A. It seems like there's two acronyms that people use here. Some people like one, some people like another. I will.

Q. Brevity is the soul of wit. So, I will use the shorter one.

You testified previously about how a POSA would have come back starting at a starting point and developing this new analgesic in 1994, right?

A. I did.

Q. You would agree that a person of ordinary skill at the time would have known many analgesics that would have been potential starting points for developing a new analgesic?

A. Yes, I would have been aware of many.

Q. I think you had a slide that indicated opioids would be one such group of compounds, right?

A. That would be.

Q. And cannabinoids would be another group?

A. That was another one that's listed.

Q. And Nsaids, I think you described as being a nonsteroidal antiinflammatory drug. Is that correct?

A. That's correct.

Q. You also described monoamine uptake inhibitors as being one of those in your study, correct?

A. Yes.

Q. And other options would have included drugs with more than one mechanism of analgesia, right?

A. Right. Yeah. When I found Tramadol, I realized that this had a dual mode of action. I'm not quite sure what your question is.

Q. It's a pretty simple one. Another option for a person of ordinary skill in 1994 in developing a new analgesic would be drugs with multiple analgesic mode of action. Is that right?

A. Yeah. Okay.

Q. You agree it would be reasonable to characterize that family of molecules as a pharmaceutical or having pharmacology?

A. Yes.

Q. For a moment I'd like to focus on opioids. And I think you talked a little about this yesterday.

As of 1994 several different types of opioid receptors were known in the art. Is that right?

A. That's true.

Q. And these receptors are proteins that are located on the surface of some cells and are relevant to the transmission of pain signals. Is that right?

A. That's correct.

Q. And the opioid receptors known in 1994 include MU opioid receptors, right?
A. That's correct.
Q. And it also included Kappa opioid receptors, right?
A. That's correct.
Q. And delta opioid receptors, right?
A. That's correct.
Q. And opioids, opioid drugs excerpt analgesia by interacting with those receptors, right?
A. I think primarily it's the MU receptor for most of these things. But, people were interested at the time of Kappa and delta antagonists to or agonist, antagonist, agonist but for, they wanted to take care of pain. So, they were looking for agonist.

But, with the idea that they might have fewer of the side effects of morphine.

Q. And the same was true for Kappa opioid?
A. Yeah.
Q. Now, that interaction process of drug interceptors I think you described physically yesterday with your hands as being a complementarity of three dimensional shape. Is that right?
A. I don't know if I used those words but that's correct.
Q. And people often analogize that to a lock and a key where the lock has given shape to fit a particular key and not

other keys, correct?

A. Yeah. I think that's a bit simplistic in looking at it because neither the lock nor the key is rigid. So there's some induced, there's adjustments that occur with a lock and a key.

Those are both very rigid and there's no adjustments that can be made. But, yeah, so I would say there's another model of that that is sort of the induced fit model that describes, it allows for the slight changes in structures of both the receptors and the small molecule.

Q. Now, would you agree that as of July 1994 there were opioid compounds that were known to target more than one type of opioid receptor at once?

A. Right. I mean we saw yesterday that Tramadol does. I didn't discuss that. I sort of whizzed by it. But, there were data in one of those papers, I think one of the Raffa papers, if I remember, where he pointed they did test binding affinities of those other receptors.

Q. Is it your testimony that binding affinity is predictive of functional analgesic activity?

A. This is definitely not predictive of function.

Q. Now, could we have PTX 139 up which is Raynor and it should be in your cross binder.

A. 139?

Q. 139. Now I think that we had not talked about this one before. You reviewed this article in the course of

formulating your opinions in this case, right?

A. You know, if I listed it somewhere, I've looked at a lot of references and I may have looked at this one. This may, I honestly don't remember.

Q. I represent to you, sir, that you cited this report.

A. Okay.

Q. I believe in your July expert report.

A. Okay.

Q. If I could have Page 4 of this document up and can you blow up Table 1.

Looking at Table 1 of this document, which is on Page 4 of PTX 139, you see here listed several different types of opioid interacting drugs, correct?

A. Right. Could we have the, I mean these columns represent the different receptors, right, MU, delta, right? Kappa, delta and MU, I guess. Okay.

Q. Yeah. And several of these compounds are described as being selective for either the MU, the Kappa or the delta opioid receptors, correct?

A. Well, I don't know that they are described that way. But if you look at the table, you can see that there are some that are much more selective than others. Certainly these compounds about halfway through where these numbers are greater than what, a thousand? So, yes.

Q. In fact, those compounds are described as "MU selective

compounds", right?

A. Again described that way, the table suggests that that's the case, yes.

Q. The authors describe them that way?

A. I have to take your word for it because I'm not looking at their wording.

Q. Actually you are looking at their wording, right? It says, "MU selective compounds".

A. Oh, I'm sorry. I'm sorry. I didn't see that part of the table.

Q. That's fair. So it does, in fact, indicate these are MU selective compounds?

A. I'm sorry, I thought we just had a list of compounds.

Q. No problem. And in fact other compounds are listed as Kappa selective compounds, right?

A. I see that, yes, now.

Q. And others are delta selective compounds?

A. I see that also.

Q. And then there's a group of compounds called non selective compounds,.

Do you see that?

A. I see that.

Q. And do you understand non selective in this respect to mean that these compounds interact with more than one of the MU opioid receptors?

A. That's not really what the table shows because there is, there are several compounds that don't appear to interact with any of them.

Q. Okay. So, let's pick out one. Etorphine, would you agree that it interacts with all three of the receptor types?

A. Etorphine I think is the one, not Pentazocine. But Pentazocine is also the one he highlighted as also interacting with all of them.

Q. In fact, with the exception of let's say three of these compounds where every number is greater than a thousand, all of the compounds interact with more than one of the opioid receptor types, correct?

A. Yeah, that's true. They interact, yeah.

Q. Now, so these compounds that did interact with more than one receptor exhibited multi-analgesic mechanisms of action, right?

A. Well, I'm not sure that's true. Naloxone is an antagonist. So, I don't think that exhibits analgesic activity.

Q. Now, but some of these compounds do obviously interact with multiple of the receptors. And you know them to be analgesics, right?

A. Yes, I think Pentazocine is one and Etorphine is another. Leu-enkephalin are, to my knowledge, not used as drugs. But, those are some that I recognize. Naltrexone may

be an antagonist too. I don't know exactly what all of these things are.

But, I do know Pentazocine and Etorphine are analgesics. I think Etorphine is the compound you use to knock out elephants, if I remember.

Q. You did not -- you said that a person of ordinary skill in 1994 would have been motivated to find compounds with multiple mechanisms of action, right?

A. Yes, polypharmacology.

Q. But you did not start with any of these compounds in your exhibits, correct?

A. I guess what you are trying to get me to say is I am characterizing this as having polypharmacology. These compounds are interacting. And all these receptors in my mind, in my view, the polypharmacology of this of having multiple modes of addressing pain would be rather different mechanisms than just opioid. I can't tell you that.

Let's pick any compound that has these multiple activities. I don't know if Pentazocine is an example since that's the one that's highlighted. I don't know if there is analgesic activity arising from each of these modes of interaction.

So I really don't know if analgesia in these compounds is arising because of interactions at these different receptors. These compounds could be antagonists so Pentazocine

may be an agonistic MU. But it may be antagonist to delta and Kappa.

So in that case in my mind the analgesic activity is not arising from polypharmacology. So without knowing all of that information and whether analgesia is arising from each of these interactions these compounds have with the different opioid receptors, I can't say that there's polypharmacology here that would be beneficial in terms of creating a new analgesic.

Q. Is it fair to say then that you didn't perform such an analysis? You did not look at these compounds interacting with more than one opioid receptor to determine whether in fact they exhibited polypharmacologic analgesia, correct?

A. No, I didn't. No. I was looking for something a bit -- I was trying to get my mind, you know, the opioid is the classic compound and very good analgesics. But, they are notorious for having bad side effects.

I think I just saw in the paper this morning that doctors are not supposed to just prescribe opioids for chronic pain anymore because of the addiction potential that you have. So, one wants to minimize opioid side effects.

Q. Now, it's fair to say you're not an expert in treating pain, correct?

A. I think that would be an M.D. that would be an expert in treating pain, yeah.

Q. So you are not, right?
A. I am not an M.D., no.
Q. And it's your testimony, sir, that FDA has withdrawn approval for the use of opioids to treat chronic pain?
A. I didn't say that.
Q. You said?
A. Well, I said, I just read the headline this morning that doctors are being told not to prescribe it. I don't think this is from the FDA. I don't think I said that, did I? I don't think so.
Q. So, would you consider what the FDA says about the use of such compounds to be influential in determining what a person of ordinary skill would choose as a starting point for creating an analgesic in 1994?
A. The FDA would be one agency. I mean any, I don't know, approved drugs generally are good. Not all drugs start off in this space. Many of them start off in Europe and come here. I think some start here and go to Europe.
Q. And you know as a matter of fact, don't you, that Tramadol was not FDA approved in 1994, correct?
A. Right. But it had been approved in Europe for many years. So clearly it had an established safety efficacy track record.
Q. And that record was insufficient to get FDA approval at least for more than a decade, correct?

A. I have no idea.

Q. Well, how long was Tramadol in use in Europe, since you just testified?

A. I don't know exactly when its use started. But, it was certainly well before 1994. Since I have not looked at records or anything, I really don't know whether Grunenthal ever tried to get it approved in the United States. I have no idea of what was done there. I mean ultimately it was approved, but, I don't know what the hold up was.

Q. Now, at the beginning of your testimony yesterday you discussed the general idea of structure activity relationship determination or SAR, correct?

A. That's correct.

Q. And you also mentioned having obtained one or more patents, right?

A. Myself personally?

Q. Correct.

A. I'm an inventor. I'm listed as an inventor on some applications. I think I said that none of these patents have issued yet. So, it hasn't gone through the process of the examiner raising questions or addressing the questions. So none of that process has started on any of the patents that I'm an inventor on in the last couple of years, no.

Q. And those patent applications for all of them you signed an inventor's oath, correct?

A. Yes, I did.
Q. And that said that you had reviewed the applications and attested to its correctness to the extent of your knowledge, right?
A. That's correct.
Q. And so you viewed what you had in those applications as patentable, correct?
A. That's correct.
Q. And were those applications a result, any of them, of SAR studies you performed?
A. Yes, they were definitely the result of some SAR studies, binding studies, yes.
Q. Now, you would agree with me in this case you have not identified a single starting point for the development of a new analgesic in 1994 but rather multiple starting points, right?
A. I'm sorry, could you repeat the question?
Q. Sure. You would agree with me, wouldn't you, that in developing your opinion of obviousness in this case, you do not start with a single starting point that a person of ordinary skill would have used in developing a new analgesic in 1994, but rather multiple starting points, right?
A. I think where I ended up was starting with Tramadol.
Q. And Tramadol is composed of multiple molecules, correct?
A. Well, I think it's composed of two enantiomers, yes.

Q. And I believe you've testified that the metabolite of those enantiomers would also be relevant, correct?

A. Right. They were known metabolites. They were known to be active.

Q. In fact, the same is true about the racemic mixture of the Tramadol enantiomers, right?

A. That what?

Q. Well, you would agree with me that you have testified that in your view a person of ordinary skill would have been motivated to select first off either enantiomer of Tramadol as a starting point in 1994, right?

A. Yeah. I think what we did is we went through the analysis where we looked at all of those. We considered all of those. And we found good things. And then all of the prior art ultimately led to a single compound minus O desmethyl.

Q. Sorry.

A. I'm sorry, I interrupted you.

Q. I interrupted you. So, let's try it again.

So, isn't it correct that in your view a person of ordinary skill would have been motivated to select either enantiomer of Tramadol as a starting point in 1994 and developing a new analgesic?

A. They would have been among the ones that were considered, yes. I think I testified though that of those

two, the RR had the kind of properties that a person of ordinary skill would look for, namely that it had this polypharmacology.

Q. So, is it your testimony, sir, then, that the SS would not have been a good starting point for a person of ordinary skill in developing an analgesic in 1994?

A. No. I'm just saying I think I said they would all be starting points. Some were better than others, I think. But, they would all be ones that I think that one would look at.

Q. When you say they all, are you including each of the enantiomers of Tramadol? Each of the enantiomers of Tramadol's O desmethyl metabolite, as well as the racemic mixtures of both of those enantiomers?

A. I think I made that clear in my opening reports and that's what we discussed.

Q. I just wanted to make clear for purposes of the record because I think that's correct.

You would agree with me, and I think that you just testified that, and going through your analyses, you then later honed in on one of the stereoisomers of O desmethyltramadol as one of your more interesting starting points, right?

A. I honed in on it makes it -- what I think I testified is the prior art led me there.

Q. Okay. So, and one of the reasons you cited was that in your view some people could not metabolize the Tramadol

enantiomers themselves correctly. Is that right?

A. Yes I think that was documented in the literature several places.

Q. You cited no such literature in your testimony, right?

A. I don't remember whether it got cited or not. There's something in Parr which was not part of this. This is something from Sevchek (ph) which discusses this. So certainly we didn't discuss the par reference at all. But we did discuss the Sevchek reference.

And I don't remember whether we talked about that part of it or not. But, I think I made the point when I was down there that not all people have, they have a full suite of enzymes to do these metabolic transformations.

Q. Let's talk a little bit about that. So, you would agree with me, wouldn't you, that O desmethyltramadol was known to occur in man only to a minor extent?

A. That sounds almost like a quote.

Q. In fact it is.

A. Yes, I would agree.

Q. So, let's bring up Sevchek which is DTX 736. If you would focus on in this paragraph right here, and here, would you agree with me that Sevchek reports on desmethyltramadol is -- well, actually, why don't you just read the first sentence into the record, please.

A. Okay. Although O desmethyltramadol is the main

metabolite of Tramadol in most species, in man there is only a slow biotransformation and Tramadol is excreted mainly unchanged.

Q. Could you also read the next sentence?

A. Sure. Hence the production of metabolites with strong opioid activity, i.e., O desmethyltramadol occurs in man only to a minor extent.

Q. Now, this phenomenon that O desmethyl Tramadol occurs in man only to a minor extent would have been true both for people having normal metabolites and also this a cytochrome P450 chromosome, correct?

A. I don't know. It would certainly be true of people that had reduced cytochrome P450 activity. Whether a cytochrome P450 was important, I don't know if it's generally true of all people though. I don't know how broadly. I don't know what population of people they looked at. I don't know anything about that.

But clearly at least sometimes it doesn't get metabolized. And certainly those people, some of these people would not have the enzyme or have low amounts of it. I can't speak to the rest of it though.

Q. And the article simply reports that in man in general this transformation O desmethyltramadol is minor, correct?

A. In general it's not there.

Q. Well, in man it's there, correct?

A. In man, it's there.

Q. There's no indication that only people having incorrect cytochrome P450 activity were measured in this study, right?

A. There's no information about that. Maybe if we go to Lintz we would find that. I don't know. But, yeah, that's fair. That's all the more reason to actually start with the compound that doesn't have the methyl group there.

I mean if it is, in fact, true, which you're suggesting is true more generally than I necessarily interpreted this, that clearly motivates a person of ordinary skill to start with the compound without that methyl group because then you wouldn't rely on metabolism as a mode of giving you the more active analgesic activity.

Q. Well, you would agree with me that prior to 1994 there were no studies in man in which only the O desmethyl metabolites or a mixture of the two metabolites was administered to obtain analgesia, correct?

A. I will say that I'm unaware of any, yes.

Q. And in fact every study which you are aware of in which some component of Tramadol was administered to patients, was simply the two enantiomers of Tramadol, correct?

A. Yeah, that's correct. I don't even know if the individual enantiomers were administered separately. And so, yeah.

Q. Now, let's talk a little bit about Tramadol. The two

enantiomers, I believe you discussed this in your direct testimony, are, of Tramadol, are mirror images of each other. Is that correct?

A. That's correct.

Q. Could we have my demonstrative Number 1? Are these the two enantiomers of Tramadol?

A. Yes, I believe so. Yes.

Q. I believe you testified that you're unaware of any clinical studies in man in which only one of the two enantiomers was administered and observed for analgesia, correct?

A. That I'm unaware of any.

Q. Now, by July 1994 therefore a person of ordinary skill understood that the overall antinociceptive activity of Tramadol deprived the complementary and synergistic activity between these two enantiomers, right?

A. I think we may be coming to a Raffa reference. But, you would certainly know that based on the prior art. Maybe you should rephrase the question.

Could you just rephrase the question before I answer? Sorry. I may go off on a tangent here. So, let me get your question again, if I may.

Q. Sure. So, by July 1994 a person of ordinary skill would have understood that the overall antinociceptive activity of Tramadol was derived from its complementary and synergistic

interaction between the two enantiomers?

A. In man?

Q. In man.

A. I'm not sure they would have known that. There was, there were data in animals that suggest that, certainly.

Q. Right.

A. I don't know that there were any data in man that support that.

Q. And so is it fair to say that if you don't see data in man, in a piece of prior art that you are referencing, that you discount its value as a predictor for a person of ordinary skill in 1994?

A. I didn't say that. I answered your question which was different. You asked me basically is the drug that means in man now, then the other references that we have, certainly enlighten us as to possibilities and how these may be working in man. But, the actual tests for what you are saying, as far as I know, were not done in man. They were done in animals.

Q. And the tests that you discussed in Driessen, both of the Driessen references and both the Raffa references and the subject reference and so forth, I think you had a slide of a bunch of references?

A. Right.

Q. None of those were done of man, correct?

A. No, they were done in animals. And they were decent.

That's a decent animal model. But, it doesn't say it works that way in man.

Q. In general you would agree with that?

A. It suggests that this is a mechanism of action in man. That's all the information that you have. And so I think that's what you would say is that's probably that way in man.

Q. Okay. Could we have up the Raffa two article which I think in your binder from yesterday is DTX 692. You may have a copy.

A. I do have a copy in yours.

Q. You are familiar with this because you discussed this yesterday?

A. Yes.

Q. The title is Complementary and Synergistic Antinociceptive Interaction between the Enantiomers of Tramadol, correct?

A. That's correct.

Q. Now, I think yesterday you focused on the abstract of this article. And I believe Mr. Capuano attempted to focus only on the left side of it.

Do you remember that?

A. I remember that's where we focused.

Q. Why don't we look at the whole abstract and have what I think is called Harvey called the rest of the story.

You would see here that, in fact, the abstract

discusses how the plus and minus enantiomers produced antinociception in a synergistic way, correct?

A. Right. So probably we should highlight so it's on the right half.

Q. Let's highlight synergy there.

A. It suggests based on this that's what it says, yeah.

Q. Could we also highlight significantly more potent, etc than the theoretical additive effect of the enantiomers.

Now, would you agree with me that in this paper the authors examined separately the analgesic activity of plus Tramadol and minus Tramadol in your model?

A. I believe that's right. That's what we said yesterday. Right. So, that's reflected in Table 1 that we did discuss.

Q. Right.

A. It's also in Table 2.

Q. Okay. And the authors then prepared a theoretical additive effect which is discussed here in the abstract, right?

A. That's correct.

Q. And what the authors found was racemic Tramadol i.e. Tramadol having both enantiomers was significantly more potent than the theoretical additive effect of each enantiomer, right?

A. Well, I think you have added some words but I think you represented it fairly. Okay. Sorry, I was on the wrong line. Okay. Yes.

Q. I have represented it fairly? You agree?

A. Yeah.

Q. Now, and in fact there is some P values noted here. Do you see those?

A. Yes.

Q. And P values are measures of statistical significance, correct?

A. They are.

Q. And as a scientist in general you are familiar with the notion of P values, right?

A. I am.

Q. In general a P value of less than .05 as indicated here means that there's a 95 percent chance that the observed effect was not due to random effects, correct?

A. Right in whatever experiment was conducted.

Q. Now, and in English that means these data showed that the synergy was statistically significant, correct?

A. That's right. That's what's being presented.

Q. Now, could we go to Page 9 of this document at the lower right hand? And could we blow up the bottom of this column and the top of this column? You can put them on top of each other because they are a single paragraph.

You see this paragraph in summary, correct?

A. I do.

Q. Now, about midway down this paragraph I think on the screen it's here starting with our conclusion, could you read

that sentence in the record?

A. Sure. Our conclusion is that the overall antinociceptive action of Tramadol derives from the combined pharmacologies of the two enantiomers of the racemic drug.

Q. Tramadol apparently results from the fortuitous interaction of the enantiomers, right?

A. That's what this says.

Q. You agree with that conclusion, correct?

A. Not entirely.

Q. Well, the authors had that conclusion, correct?

A. That's correct. But if you look at the Table 2 -- are you going to go there?

Q. We can in a moment.

A. Okay. So, that's what the authors are saying, yes.

Q. Right. And these are Grunenthal authors, are they not?

A. I believe. I have to look. There are some papers which I don't know. There's an R.W. Johnson so, yeah, so some of the authors were Grunenthal for sure.

Q. And Grunenthal knew, more than anyone in the world, about Tramadol. Is that fair?

A. I think that's probably fair, yeah.

Q. Now, not only does the analgesia result in synergy but the sides effects result in, either it results in no synergy or put differently -- let me clean that up. Withdrawn.

Would you agree with me that the side effect profile of

Tramadol was shown to have simply additive or counteractive effects between the two enantiomers versus the racemic mixture?

A. Yeah. I mean these side effects are the non antinociceptive things and elsewhere in the article in the table it presents that, so, yeah.

Q. And would you read the sentence beginning Hence into the record please?

A. Yeah. Hence, the clinical profile of Tramadol apparently results from the fortuitous interaction of the enantiomers on the therapeutic endpoint analgesia, but not on side effects.

I did emphasize the word "apparently" because there's equivocation there, I think.

Q. Well, you read the author's conclusion, correct?

A. I did read the author's conclusion.

Q. They didn't qualify it in any other way?

A. Other than saying apparently, no.

Q. Aren't the observed reports in any paper apparently what is observed from the experiments reported?

A. I have no opinion on that.

Q. Now, let's go to, you testified yesterday that a person of ordinary skill would have been attracted to Tramadol as a starting point for developing a new analgesic because it had a dual mechanism of action, right?

A. I did.

Q. And in your view Tramadol was unique in this respect, correct?

A. I think it was characterized that way in the prior art, yes.

Q. And you would agree with me that every compound is unique, correct?

A. I would agree with that but they are not characterized as such as Tramadol was.

Q. And when you say was characterized in prior art, you are referring to what was known as the Raffa one reference, correct?

A. That's correct.

Q. You have identified no other references that refer to Tramadol as either atypical or unique, correct?

A. That's true.

Q. Now, you would agree with me that you found Tramadol "atypical" because Tramadol had no MU opioid and monoamine reuptake method of action, right?

A. I think that's how the authors of the prior art characterized it, yes.

Q. Do you agree with that assessment?

A. Yes.

Q. Do you agree with me that Tramadol's monoamine reuptake relates to the both serotonin as well as norepinephrine pathways?

A. Is Tramadol as the drug is a mixture of enantiomers?
Q. Yes.
A. Yes.
Q. And Tramadol analgesic activity results from three mechanisms of action, mu opioid agonist, nor reuptake inhibition and serotonin reuptake activity, correct?
A. That's correct. Yeah, that's the implication.
Q. So, a person of ordinary skill looking at Tramadol's starting point or any of its components, would not have been motivated to eliminate any of these analgesic mechanisms in developing a new analgesic, right?
A. I think I disagree with that. I think I pointed out yesterday that that serotonin side effects, there are some bad effects associated with binding to serotonin receptors. There are a number of serotonin receptors. So they are not all bad, but, some of them are.

And if you know they are serotonin activity, then you might want to veer away from that.

Q. Did you cite any evidence whatsoever to indicate that there were bad effects from serotonin inactivity?
A. Well, I cited the example of LSD. I didn't cite any literature. It's common knowledge amongst people who deal with serotonin anyway.
Q. There are drugs that act on the serotonin reuptake pathway, correct?

A. There are, yes. They have selected activity.
Q. And there are drugs in the analgesic space, aside from Tramadol, that interact on the serotonin reuptake pathway, correct?
A. I don't know of any.
Q. Well, you cited serotonin reuptake activity compounds on your opening, one of your opening slides yesterday as places to start developing a new analgesic in 1994, correct?
A. I said monoamine uptake so that would have included. That but I knew of the norepinephrine ones.
Q. I think the transcript will show that you also referred to the serotonin reuptake pathway.
A. As in that slide where I talked about analgesic.
Q. Correct?
A. Okay, I may have mentioned that was one of the -- well, I think I was explaining what monoamine reuptake inhibitors were. I don't remember the exact context but I think that what I was doing was explaining what monoamine reuptake meant in response to a question.
Q. Now, could we look at the -- well, you would agree that pain perception was modulated by the serotonin pathway, correct?
A. Yeah, that was an element.
Q. Why then do you focus on removal of the serotonin reuptake pathway rather than, for example, the MU opioid

pathway from Tramadol and developed a new analgesic? Is it because the resulting compound had looked more like Tapentadol?

A. No, no.

Q. So you recall testifying yesterday about a criticism of your opinions as being that they were driven by hindsight, correct?

A. Yes, I do remember that.

Q. And you testified that that is not correct, right?

A. I testified that way, yes.

Q. You agree with me before rendering your opinions in this case, you reviewed the '593 patent, correct?

A. Before?

Q. Before coming to your opinion of obviousness in this case, you reviewed the '593 patent, correct?

A. I didn't review that in the context of obviousness. I saw that much later I was asked to think about this without having seen that.

Q. You were asked, so, let me understand your testimony.

Were you asked to determine the obviousness of the claims of the '593 patent without having reviewed those claims?

A. Okay. So, no. I had to review the claims to have come to that conclusion.

Q. I agree with you. And some of those claims specifically layout Tapentadol, correct?

A. Yes, some of them do of course.

Q. And prior to formulating your opinions in the case you understood that the case concerned Tapentadol, right?

A. Okay. Yes.

Q. Now, we've talked a fair amount about polypharmacology.

Would you agree with me that polypharmacology, in addition to potentially generating analgesia, also generates side effects?

A. Sure. I mean every interaction can result in some side effects. But, the idea here is is if you've got polypharmacology, I think I explained this, at least let's, if we can focus on this particular situation where we're talking about analgesia and pain, the opioid, you know, they are great analgesics, as I said.

And the problem with these analgesics is they are highly addictive and they have a lot of these bad side effects. So, if you could administer a lower amount of a compound that's effecting that particular receptor or if the compound you're using has a lower influence, let's say, on that opioid receptor, then you tone down that opioid activity, you presumably tone down the side effect profile, and you still maintain analgesia, the amount of analgesia that you want via this other mechanistic pathway.

Q. Now, you recall -- can we clear the blow ups, please? You recall yesterday focusing on Table 1 of this document.

So, could we look at that on Page 4? Now, this table

includes so called KI values for, among other things, racemic Tramadol and plus and minus Tramadol enantiomers, correct?

A. That's correct.

Q. And KI values are measures of the binding affinity that is observed for these measured compounds versus these various receptors, correct?

A. That's correct.

Q. Receptors that are viewed are MU, delta and Kappa opioid receptors, as well as norepinephrine reuptake receptor and serotonin reuptake receptor?

A. That's correct. Can I see my demonstrative Number 2? Now, again we have the two structures of the plus and minus Tramadol which we discussed earlier. At the bottom I've carved out just Table 1 and highlighted it.

Does it look accurate to you

A. The table is accurate. You have carved out certain things and it looks, I'm not sure exactly what you're carving out.

Q. For the moment I simply mean the table.

A. Okay.

Q. And these KI values, a smaller number indicates tighter binding to that particular receptor, correct?

A. That's correct.

Q. Now, you see here that plus Tramadol has a tighter binding than minus Tramadol to the MU opioid receptors, right?

A. That's correct.

Q. By something in the neighborhood of 15 to 20-fold, right?

A. That's true.

Q. And it also, it being plus Tramadol also has a tighter binding to the serotonin reuptake pathway than does minus Tramadol, correct?

A. Yes, that's true by a five-fold difference.

Q. And conversely minus Tramadol has a tighter binding to the norepinephrine reuptake pathway, correct?

A. Minus Tramadol has a tighter, yeah, okay, it has the tightest binding, yes, of the three.

Q. And again something in the neighborhood of six fold, five to six?

A. Five relative to the plus enantiomer, but to the mixture it's not even a factor of two.

Q. Right. Relative to the mixture, relative to plus Tramadol minus Tramadol, about a five yield tighter binding, right?

A. Right.

Q. I believe you testified that molecules have particular three dimensional shapes, right?

A. Yes.

Q. And they have some flexibility, I think you mentioned this earlier, they have some flexibility in terms of their

three dimensional shape, right?

A. That's true.

Q. Different molecules have different amounts of flexibility. Is that fair?

A. Sure.

Q. I believe you testified that the cyclohexane ring brings rigidity to the structure of its component compounds and their metabolites, right?

A. I don't know that I said, I don't know that I said it that way. The cyclohexane ring itself is also flexible. This part it pre-organizes. I think I said these groups. And there's a preferred orientation that the cyclohexane ring enforces. But, I didn't characterize the cyclohexane ring as being rigid, I don't believe.

Q. Well, the transcript will answer that question. But let's use your term pre-organized. I think that's fair.

So, would you agree with me that plus Tramadol based on the data here in Table 1 is pre-organized, as you put it, in a shape that corresponds to the shape it has when bound to the MU opioid receptor?

A. Well, I mean we don't know exactly what it looks like when it's bound to the MU opioid receptor. Usually, as we talked earlier, this is this induced fit and so we don't really know exactly how it binds.

Q. Well, is it at least correct that the plus Tramadol

enantiomer is pre-organized in a shape that corresponds to its complementary MU opioid receptor more so than minus Tramadol?

A. What I would say is the confirmational space that's available to plus Tramadol, the low energy confirmational space, it's available to it, enables it to better interact with the MU opioid receptor than the confirmational space which is available to the minus isomer.

So, the net result is yes, as you say it. But, I think it's a little more complicated than just the way you put it. The conclusion is the same, yeah, basically.

Q. Okay. And with regard to norepinephrine, would you agree with me that the minus Tramadol molecule is more closely pre-organized to bind to the norepinephrine receptor than is plus Tramadol?

A. I really don't like the use of the word "pre-organization".

Q. You used it.

A. I have used that word, yes, in the past.

Q. A minute ago.

A. Yeah, I did. But, I think what's important here is, you know, there is a preferred confirmation and solution. And we can kind of work from that on. I think what I would say is that the minus Tramadol molecule for its the pharmacophore and the three dimensional arrangement and the flexibility that's inherent in that is better suited for binding at norepinephrine

center than is the plus isomer.

I think I pointed out when I played with these molecules, at the end I said there is flexibility here. And I said, and I said that the flexibility that's inherent in the cyclohexane molecule is the same kind of flexibility that's going to be available to the open chain molecule.

So I acknowledge then at least implicitly I think that there is likely to be some flexibility involved in the actual binding of that.

Q. Well, you would agree with me that the cyclohexane molecule Tramadol is less flexible overall than the linear compound that you modeled?

A. I would say that that's fair.

Q. And would you agree with me that pre-organizing these ligands in a manner that corresponds with that biologically active confirmations would generally be thought to lead to higher association constants to their receptors?

A. That's a general thought but it's wrong.

Q. Well, that's the general thought of a person of ordinary skill in the art, correct?

A. I think we had this discussion at my deposition and with that Bartlett article, if you remember. And we talked a little about intricacy of binding and so forth. And in the Bartlett papers of that time he notes that there are certain caveats to this and you can't entirely rely on that concept.

So, even at that time there were known caveats to saying that. If you pre-organize a molecule in the wrong way, it's not going to be able to adopt the three dimensional orientations that it needs to adopt.

And it may be, and that's part of my what I said is at least in going from the Tramadol with the six membered ring to the more flexible molecule, I suggested that what we might be trying to do here is to optimize interactions at both the opioid and the norepinephrine receptors.

And you can gain that ability by endowing the molecule with a little more flexibility. And we all, I mean I have also provided evidence in this case that showed that the flexible molecules actually bind better.

And so the answer is that pre-organizing molecules, and it was known at the time, does not always lead to better binding.

Q. Well, but, it was generally assumed, you would agree, that pre-organizing a flexible molecule in the three dimensional confirmation it adopts and bond to its receptor would provide a derivative having increased binding affinity, would you not?

A. I think that the literature, there's literature that stands in opposition to this. And I think I provided that in, I don't remember which of the reports it was, but, I did provide that. There's the DiMaio (ph) reference if I recall

correctly and it was with enkephalin.

Like I said, if you get the -- and similarly the whole opioid, the whole as I pointed out yesterday, the whole history of simplifying and making derivatives of morphine, I won't say they always lead to less more flexible molecules, but very oftentimes it leads to more flexible molecules. So there's nothing, there's no magic about the pre-organization.

Q. Well, thank you for that explanation. But, I was asking a much simpler question which is was it generally assumed, generally assumed that pre-organizing a flexible molecule in its bound state, in its three dimensional bound state as it would be at its receptor, would increase binding affinity.

A. It was but if you read, there are caveats to that, as I explained. And at that time there were known caveats that people were aware of.

Q. And the caveat you just described is that if you organize it in a way that you know interacts poorly, that could reduce affinity. Is that right?

A. I think the caveat more generally is I mean this is a process. It's not so simple as just focusing on where you go. The process is one of taking a receptor and a small molecule and they are over here and, you know, they are in whatever environment they are in and then putting them together.

It's kind of a process where you form the complex.

And the difference, in other words, the KI is determined about the relative energies of these two states, right. And so the additional caveat that you have to put in here was certainly understood by people who thought about it was that the flexible and the constrained molecules have to interact in the same way not only with the protein, which is to your suggestion, but also with the solvent.

So the simple approach that you are taking and the simplified way you're looking at this question is certainly the way that some people looked at it. But some people understood that that wasn't a reliable way of looking at it even at that time.

Q. Well, it was a general assumption at the time, was it not?

A. It was a general -- I would certainly not argue with you that it was a general, it was a generally applied paradigm in drug discovery. The other flip side of that, of course, is that, and it's also implicit, that trying to get the dual pharmacology is when you make compounds more rigid. They can be more selective.

And so in that DiMaio reference that I referred you to when we had this discussion at my deposition, in those cases the molecules that were constrained, the enkephalin analogs that were constrained had better selectivity for, I forget which the MU or I forget which ones, but they had better

selectivity for the different opioid receptors, but they had lower affinity.

So, I mean there's literature, the prior art literature at the time this was done that says pre-organizing things is not necessarily good. And these cases you don't know what the bound confirmation is so that's the problem.

Q. And so you have to make the compound and actually try the binding experiment to determine whether the compound will in fact have negative interactions, correct?

A. Well, what you determine is whether it binds as well, yeah. That's what you determine. You find it binds either if you're doing a simple receptor binding assay, what you find out is that the change you make, it binds better or worse, and these are nice examples.

If you go from plus Tramadol to minus Tramadol, that's a change. And then you do these binding studies, this is the effect of making that change.

Q. And apriori, you would agree with me that if you, in fact, confine a ligand to its pre-organized state, the state that it will have when it's bound to a receptor, that you would expect that compound to have higher binding affinity than a more flexible compound, correct?

A. Again, I think you have to think of the process you're focusing on, the end result. And you're focusing only on the ligand. You are not considering the protein. You are not

considering the interactions that the small molecule has to solvent

Q. I am considering all of those. I am saying apriori, a person of ordinary skill, would expect that a molecule that is rigidified in its bound confirmation, in a confirmation that will interact well with receptors would be expected to have a higher binding affinity than a more flexible compound. That's all I'm asking.

A. Okay. I think if everything worked exactly the way you say it, that's true. But, again, we don't know the structures of the receptors here. So, we don't know what that confirmation is.

Q. You only have sort of binding data effectively about those compounds with their receptors, right?

A. That's what we have here, yeah.

Q. Could we go to -- we can either take a break or I can push through.

THE COURT: You know, actually the court reporter has requested a break so that's perfect. Thank you. About 5 or 10 minutes.

I will remind the witness you are under oath and you are still testifying. So you're not going to be speaking to your Counsel about your testimony.

With that, we will be back in about 5 or 10 minutes. Thank you.

(Whereupon a short recess was taken.)

(In open court at 11:34 a.m.)

THE COURT: So, we are back on the record with Professor Martin and we are engaged in the cross-examination.

MR. BEST: Can we page forward one? That's it.

BY MR. BEST:

Q. Hello again, Dr. Martin.

A. Hello, Mr. Best.

Q. Now, yesterday you discussed, and I think maybe even a little bit this morning, this slide which lists certain norepinephrine reuptake inhibitors, correct?

A. Yes.

Q. And you discussed certain structural characteristics that these compounds have, correct?

A. I did.

Q. And you would agree that at least certain of the tramadol components and/or its metabolites have norepinephrine reuptake activity as well, correct?

A. Yes.

Q. Now, would you agree that you provided no data or evidence that tramadol actually binds the norepinephrine receptor at the same location that any of these compounds that you have on your slide bind?

A. I think there's no way of knowing. Well, I don't know if there's a way of knowing. I don't know.

Q. Now, we've discussed the goal of -- the goals of a person of ordinary skill in 1994 involved in a new analgesic, and we've talked a lot I think about efficacy, so can we talk a little bit about safety. Regarding safety, would you agree with me that no drug is completely safe?

A. I would agree. I've heard people characterize drugs as toxic substances with beneficial side effects.

Q. And, in fact, all drugs have side effects, right?

A. I think that's true, yes.

Q. And regarding side effects, you are familiar with the distinction between on-target side effects and off-target side effects?

A. Yes.

Q. And is it fair to characterize on-target effects as the biological responses occurring from interaction with the desired target that yield functional problems?

A. Yeah. Certainly, yeah, you can have too much. Yes, yes.

Q. And off-target effects arise from the same compound interacting with targets other than the desired target; is that right?

A. That's correct.

Q. Now, would you agree with me that no compound binds cleanly to one and only one target?

A. I will say I'm not aware of one.

Q. That's fair. Now, could we go to your -- I'm sorry, my demonstrative number 3. We discussed this morning this question of if, in fact, one started from O-desmethyltramadol, the idea of making a linear compound out of it; do you recall that testimony?

A. Yes.

Q. And in the context of that testimony, we discussed cleaving certain bonds and removing carbon atoms, correct?

A. We did.

Q. Now, at the lower left you see I've drawn a structure which is the same as the structure up here in the middle, both of which are O-desmethyltramadol, and I've numbered the carbon atoms in the cyclohexane ring; do you see that?

A. Yes, I do.

Q. And the carbon attached to the phenol is labeled carbon 1, and then counting clockwise around to 1, 2, 3, 4, 5, 6 where carbon 2 is attached to the dimethylamino methylene moiety. Do you see that?

A. Yes.

Q. Now, in the context of that, would you agree with me that a person of ordinary skill, if he or she wanted to make a linear compound out of this, had five bonds that could have been cleaved to do so?

A. You mean if we -- well, there are six bonds that you can cleave. Are you excluding what -- the bond between 1 and

2?

Q. Correct, I am.

A. Okay. Yeah, then there would be five.

Q. Now, effectively cleaving one of these bonds, and I say effectively because you wouldn't necessarily start with this compound on the slide as a starting material, but we can formally call it cleaving the bond. Do you understand that?

A. Yes, I understand.

Q. So, if one effectively cleaved any one of those five bonds, the bonds between carbons 2 and 3, 3 and 4, 4 and 5, 5 and 6, or 1 and 6, would you agree with me that simply cleaving that bond would not yield tapentadol, correct?

A. That's correct, because we have that hydroxyl group at carbon 1.

Q. That's fair. And let's assume that the hydroxyl group was replaced by hydrogen. Take that assumption.

A. Okay.

Q. Would it also be the case that were one to cleave any one of those bonds that I indicated, one would not obtain tapentadol?

A. That's true.

Q. Now, in fact, a person of ordinary skill would have to remove a carbon atom to obtain tapentadol, correct?

A. Right, from -- right.

MR. BEST: Now, could we click forward?

BY MR. BEST:

Q. Now, one of those options is this bond between carbons 1 and 6; do you see that?

A. Right. This is the -- this is the option in the first line going to the left; is that what you are referring to?

Q. Correct, correct.

A. Yes.

Q. And you might recognize this image, it was in one of Dr. Rausch's reports, more or less. I have added a couple of flourishes.

A. Okay. Well, I'm not sure I recall any images from his reports as I sit here, but...

Q. Okay. Fair enough. But you reviewed his reports?

A. Yes, I did.

Q. Now, would you agree with me that cleaving the bond that I have indicated as A between carbons 1 and 6, there is no way to obtain tapentadol from cleavage of that bond?

A. That's true.

MR. BEST: Now, could we click forward?

BY MR. BEST:

Q. Is it also true that cleaving bond B between carbon 6 and 5, again there's no way to obtain tapentadol?

A. That's true.

Q. Now --

A. Just by cleaving, yeah.

Q. Fair enough. And even if the hydroxyl was a hydrogen --

A. But if I removed a carbon, we could get there ultimately. Never mind. Sorry. I apologize.

Q. Sure. By that do you mean that you could sort of work backwards and then add some more carbons in; is that the point?

A. No, no, no. I was anticipating other things. I'm sorry.

Q. Okay. Fair enough. So, you would agree that cleaving bond B would not yield tapentadol, correct?

A. I agree.

MR. BEST: So, let's click forward.

BY MR. BEST:

Q. Now, bond C, this one is interesting because once you cleave bond C, I think you have already testified, simply cleaving the bond would not yield tapentadol, but then you would have two options for removing a carbon, either what's been labeled in my diagram as carbon 4 or carbon 5. Do you agree?

A. Okay. Now, so we're going to start removing carbons, right? Okay.

Q. Right. And if you remove what is in red as carbon number 5, you do not obtain tapentadol, correct?

A. That is true.

Q. It's only if you remove carbon 4 that you can obtain

tapentadol through this pathway, right?

A. Right. Again, you have to remove the hydroxyl group.

Q. Of course.

MR. BEST: Let's do the next one.

BY MR. BEST:

Q. And if you cleave the bond that I have indicated as D between carbons 3 and 4, again you have two options. You could remove -- if you remove carbon, what's been labeled as carbon 3, you would not obtain tapentadol, correct?

A. Let me try that. Carbon 3 is the red one? Yeah, you would not.

Q. But if you remove carbon 2 -- or rather carbon 4, you could obtain tapentadol through that route, correct?

A. Right. That's the blue carbon, right?

MR. BEST: And the last one, please.

BY MR. BEST:

Q. And if you cleaved carbon bond between -- the bond between carbons 2 and 3 which I have labeled as E, that pathway would also not lead to tapentadol, correct?

A. That's correct.

Q. Now, you provided some testimony this morning as to -- suggesting that one of ordinary skill would not cleave either what has been labeled here as bond E between carbons 2 and 3 and between -- bond A between carbons 1 and 6. Do you recall that testimony?

A. Okay. So, I see that -- I see the bond B. Am I supposed to look for the other one that's between 1 and 6, or is that not indicated?

Q. It's not indicated in the center, but you would agree with me that you offered testimony this morning that a person of ordinary skill would not have been motivated to cleave either the bond between carbons 2 and 3 or the bond between carbons 1 and 6, correct?

A. Yeah. I'm having to look over here. Yes, but that's true.

Q. And your testimony in that respect was that this would, quote, destroy stereo centers that are critical to maintaining stereochemical control, correct?

A. Well, critical to maintaining the three dimensional relationships that are in the cyclohexane ring.

Q. And underlying that analysis, is it fair to say that you are suggesting that a person of ordinary skill would, therefore, expect the resulting compounds to have poor analgesic activity; is that right?

A. Yeah. I think they, a person would expect them to have worse activity, but it would be a guess, yes.

Q. Okay. Could we look at the Flick article, which I know we've discussed at some length yesterday and a little bit this morning, which is DTX-715 or DX-108 at your preference. I guess 108 is the English, so maybe that's better for you. I

think on the screen it's probably better to have DTX-715 because the tables are cleaner.

MR. BEST: Could we go forward one page?

BY MR. BEST:

Q. This is the Flick article that you discussed yesterday and this morning, correct?

A. Yes, that's correct.

MR. BEST: And could we look at Table 4, which is on page -- I'm not sure of the page, maybe 6. Yeah, could we blow up Table 4, please? Could we highlight, please, L201?

BY MR. BEST:

Q. Now, the compound L201 or composition, rather, is the various stereoisomers of tramadol, correct?

A. That's correct.

MR. BEST: And could we also highlight E417 and I think it's 418, maybe 419, but it is whatever is below 417?

BY MR. BEST:

Q. Now, these two compounds are identical to the tramadol composition except that instead of having an OH group at R2, they have a double bond, and that double bond is either between carbons 1 and 2 or between carbons 1 and 6, correct?

A. That's correct.

Q. And in both instances, you have removed the stereo center. In fact, in one instance between 1 and 6 you removed one stereo center, namely the bridgehead-carbon that you

discussed earlier, and the 1,2 olefin removes both stereo centers, correct?

A. That's correct.

Q. And if you look at the analgesic activity of those two compounds, do you see that, in fact, there are analgesia -- let's start with 417 -- is, in fact, better than tramadol?

A. That's correct.

Q. And so you would agree with me that a person of ordinary skill reading Flick would understand that the stereo centers at 1 and 2 in the diagram of Table 4, which I think I've labeled as carbons 1 and 2 in my diagram, were not necessary to obtain analgesia?

A. They're not necessary -- well, they removed them, and so they still had analgesic effect, but they also increased the toxic effects of the molecule. So, that's a bad thing.

Q. And for 417, that toxicity increase, the toxicity has been increased then for 418 or whatever is below it, correct?

A. Correct, relative to 201.

Q. But the analgesia of 417 is better than L201, correct?

A. That's correct, but it's more toxic.

Q. Right. And yesterday I believe you discussed the concept of therapeutic index. Do you recall that?

A. Yes.

Q. And when you discussed it, you discussed therapeutic index as being, quote, very important. Do you remember that?

A. I certainly said it was important, yes.

Q. And you see here that the therapeutic index of the tramadol composition and the E417 composition are less than twofold different; is that fair?

A. So, in the E417, that particular case, we have a single compound, yeah. So, it's more toxic, yes.

Q. That's not what I asked you, sir. What I asked you was with regard to the therapeutic index. Would you look at that column, please.

A. Okay.

Q. And I asked you, is the therapeutic index of E417 just about twofold, actually a little less than twofold worse than the tramadol composition?

A. Yes.

Q. And do you regard that change in therapeutic index, to be clear, a roughly twofold change in therapeutic index to dissuade a person of ordinary skill from making this change from L201 to E417?

A. No. I think I've said before that factor of 2 is not necessarily something that one hangs a hat on. It is certainly something to look at, and if it were twofold better, that would lead you in the direction, you would say, okay, so maybe I can do it a little bit better. So, it's not a big effect, but it is certainly a noticeable effect.

Q. Now, could we have up -- and I've had a note from my

colleagues. I believe that underneath E417 is labeled E410 rather than whatever else I've said today.

Could we look at your demonstrative number 49? Now, you recall testifying this morning about these various conformations, correct?

A. Yes.

Q. And with regard to conformation A, I believe you testified that this is the most stable conformation, right?

A. I said that's the most stable of these three, yes.

Q. And to be clear, when you say it's the most stable, it's not the only confirmation that this molecule that you represented as A would have in solution, correct?

A. You mean if I have conformer A as the way I represented this the only way, or would I have all three of these in solution at the same time?

Q. My question is the latter. Would -- in solution, you have more than simply conformation A of this molecule that is drawn on your slide?

A. Right, so you would have a mixture of all three.

Q. Now, with regard to conformation A, I believe you indicated there is this Gauche interaction between the methyl group on what is depicted as the front carbon and the -- this methyl group that is -- well, it is an ethyl side chain, but the methyl group of the side chain depicted on the back carbon. Do you see that?

A. Yes.

Q. Now, would you agree with me that if you had the compound in which this carbon, carbon number 5 --

A. Okay. I'll have to look. I'm sorry. I was not looking at the screen.

Q. No problem. Would you agree with me that if you had the compound where carbon number 5 was removed but carbon number 4 was not removed, that, in fact, you have exactly the same interaction between those side chains?

A. Yes. When I presented that as these other options for excising, I think I said that the analysis -- maybe I didn't say it, but the analysis would be the same.

Q. And in solution, would you agree with me that this methyl group that's attached to the structure you have drawn as conformation 1 would actually rotate -- it's a little difficult to do this in court -- but would rotate backward into sort of behind the plane of the screen to relieve this interaction?

A. The interaction is actually more with -- yeah, okay. So, there will be some interaction there and it would have to move a little bit somewhere, yeah.

Q. And to be precise, this methyl group would, as drawn, recede behind the plane of the screen; is that right?

A. Right.

Q. And if you had another carbon attached to what has been labeled as carbon number 4 -- or, rather, carbon number 5, if

you had another carbon attached to carbon number 5 such that you removed no carbons, had simply cleaved the bond between carbons 4 and 5, would you agree with me that that side chain would also rotate to behind the plane of the screen to relieve this Gauche interaction?

A. All right. So, now we have yet another carbon atom which is attached there as you are referring to.

Q. Correct.

A. And that is going to, as you say, move with it, and a potential issue here is that when that happens, you may place that particular carbon in a bad place relative to binding to the norepinephrine or, yeah, either receptor, actually.

Q. And you don't know whether that would be true until you actually make the compound and test it with those receptors. Is that fair?

A. That's true, yes.

Q. Now, you have drawn --

MR. BEST: Could we go forward, actually, to slide number -- or backward to slide 32, I believe, of this deck? No, it's not this. Maybe page forward one. Let's try one more. Again. Again. That's it.

BY MR. BEST:

Q. So, you discussed yesterday this notion of options, in fact, you labeled on the slide three options that a person of ordinary skill would have had starting with what you've drawn

here, an enantiomer of tramadol, and you have labeled those options as scission, excision and substitution, correct?

A. Right.

Q. Now, you discussed yesterday the notion of substitution sort of in passing, and I think you clarified that you meant adding something to the ring; is that right?

A. That's correct.

Q. And when you said that, what were some of the possible substitutions you had in mind?

A. Well, I mean, there are many substitutions. I mean there are many possibilities. There can be a whole host of things. But in making those substitutions, if that's the path you would take, you know, I don't know whether you would want big or small. It kind of depends. It can be any number of groups. There would be certain places you would probably not necessarily want to put them because they might change conformations because of bad interactions, but there are quite a few. I mean, there are a lot of different R groups out there.

Q. That a person of ordinary skill could have chosen to decorate this cyclohexane ring with?

A. Right. And I think my point was that that wouldn't be the first thing one would do because at least in the theme of looking at, let's say, opioid analgesics, this is an opioid, that the history is simplifying, not complicating, for the most

part.

Q. You discussed morphine in that context and the simplifications of the morphine molecule, correct?

A. Right.

Q. Would you agree with me that in addition to simplifying the morphine molecule, one method of SAR for a morphine that chemists have undertaken is to actually make it more complicated, particularly adding more complex groups to the free -- the amino group in morphine?

A. Yes, that's a very common thing, right.

MR. BEST: Now, can we look at Flick once more, and again probably the German for the screen, but -- which is DTX-715, but you may want to look at DX-108 in your binder because that's the English.

BY MR. BEST:

Q. Now, you have testified that a person of ordinary skill would have been motivated to convert the aliphatic hydroxyl of tramadol to a hydrogen, correct?

A. Yes, based on the results that are in this table, yes, that there was no significant loss of activity.

MR. BEST: And could we blow up Table 4 once again? I'm sorry, with the structure in it. Thank you. And could we highlight L201, that line? Can we also highlight E609, that line?

BY MR. BEST:

Q. Now, L201 I think you've testified earlier is the tramadol composition, correct?

A. Yes.

Q. And E609 is the composition having a hydrogen at the, what you called the bridgehead position in Table 4 as discussed as R2. Do you see that?

A. Yes.

Q. And when that substitution was made by Flick and his coworkers, he obtained a lower level of analgesia, correct?

A. Slightly lower, yes.

Q. And he obtained --

A. Again, if you look at the things, I think I pointed this out yesterday, if you look at what's in parentheses, there's overlap in here, but the number 16 is less than 23.6 -- or 16.1, actually, is less than 23.6.

Q. And would you agree that they also observed, with regard to toxicity, an increase in toxicity by adding the hydrogen into position R2?

A. That's correct. But again, it was only small.

Q. And you noted the parentheses with respect to analgesia. Let's look at the parentheses with respect to toxicity. There's no overlap between the range reported for E609 and the range reported for L201, correct?

A. That's correct.

Q. And the therapeutic index, which again we've talked

about earlier, as a result of the data that Flick obtained, showed a decreased therapeutic index for converting the OH at R2 to hydrogen, correct?

A. That's correct. But again, I've said the factor of 2 or 3 is not huge and wouldn't necessarily dissuade somebody from doing one thing or another. I mean, there are other changes presumably one would think about making that would -- could potentially offset that either way.

Q. Well, it's not persuasive to go toward the H, is it?

A. I'm sorry?

Q. One of ordinary skill would not be persuaded to go to an aliphatic H at R2 rather than an aliphatic OH by these data, would he or she?

A. Well, you would have better analgesic activity, and I think one of the points that I think would have captured, a person of ordinary skill, would have captured their attention, was the acknowledgment by the authors that this was a surprising result, and so this might be a fertile field for further investigation.

Q. Well, thanks for that explanation, but I think you said that there would be an increase in analgesia, but, in fact, there is no increase in analgesia from the tramadol composition to the hydrogen containing composition, correct?

A. No, I think I said -- the way I looked at it yesterday, I said they were comparable, and I think the way the authors of

the article characterize it is it had -- I think they said it had significant activity, I forget the exact wording, but I think they said significant activity, and they sort of described how they were a little surprised by that. They didn't use the word "surprised," I don't think in there, but they said it was unpredicted, unexpected, and so I think lots of times when you find unexpected things that -- when you find unexpected things, that's often a cue to look at that a little bit more.

Q. Now, thank you again for that explanation, but my question was a pretty simple one. It is correct, and I'm asking it because I think you misspoke about two questions ago in saying that E609 has a higher analgesia than --

A. Oh, I'm sorry.

Q. It does not, correct?

A. No, I did misspeak if I said that.

MR. BEST: Can we go back in your direct demonstratives to number 56? And I'm sure it is actually going to be like 57. But -- could we go forward? Could we go backward then? We only have two options. Yeah, that one is good.

BY MR. BEST:

Q. We looked at I think actually this one a few moments ago. Now, again, you discussed --

A. So, that's not --

Q. I said a similar one. It's not quite similar.

A. Yeah, I'm not sure we've looked at that before, actually.

Q. I think you're right. So, here we have conformations A, B and C once again, but here you are noting the inclusion of an OH at the aliphatic, what we've called the bridge-carbon, correct?

A. That's correct.

Q. And you note that there is an H bond between the OH and the amine, correct?

A. Okay. So, I mean --

Q. Let's start with, is that correct?

A. Well, that's based on the -- that's based on findings in Spasoff. That's not based on any information I have, and that's based on analogous compounds, not this particular one, because if you remember, Spasoff also didn't have the OR group on the aromatic ring of the top left-hand structure, and so he was looking at conformational aspects in those compounds closely related to this, but not identical. And he was the one that said that some conformations, namely the ones I've shown you, conformation A and conformation B, were stabilized, well, he referred to them as being stabilized by a hydrogen bond, and if I recall, he had some spectroscopic evidence that supported that, but I would have to go back and review that to be sure. That's my recollection. It may have been NMR. It's hard to

find the NMR. I think it was IR, but I don't remember for sure.

Q. Well, let's sort of unpeel that a little bit. Do you disagree with Spasoff that there would have been a hydrogen bond between this aliphatic OH and the amine?

A. No, that's why I put it there, is because I am assuming he was correct, and that's why I put it there.

Q. Right. And that H bond would tend to stabilize conformation A, correct?

A. Well, I think a hydrogen bond, it makes it less bad. I mean, sure, a hydrogen bond we think of as a stabilizing factor, but in this particular case, and this conformation A as well as conformation B, this hydrogen bond actually enables you to -- I think it's a six-membered ring, one, two, three, four, five, six, yeah. So, basically there are -- this oxygen, the oxygen that we have here and the attached hydrogen, so it's the hydrogen atom that's attached to the hydroxyl group in conformation A, is going to be hydrogen bonding with the nitrogen, and so that actually relieves some of the steric interactions as well. So, it actually does more than just be a hydrogen bond. And you have that in both conformation A and B. So, it's really, you know, if you look at it carefully and think about it, I think it's more than just simply the hydrogen bond.

Q. That's fair, but you would agree that the hydrogen bond

does stabilize conformation A?

A. Yeah, right.

MR. BEST: Now, can we look at the Frankus paper that you discussed yesterday, which is DTX-717? I know there's an English translation which you marked, but I don't remember the number.

MR. CAPUANO: I think it was 2052.

BY MR. BEST:

Q. 2052. So, you may want 2052 since it is English, but for the screen, could we have -- yeah, actually that's fine.

A. Is that in your binder?

Q. I think it is in your yesterday bind from defendants.

MR. CAPUANO: I think it is not.

MR. BEST: Oh, it is not? I think it is behind your -- the Frankus.

MR. CAPUANO: I'll take your word for it. Let me look.

BY MR. BEST:

Q. If you look at the Frankus article, which I think is tabbed at 717, do you actually have two documents there, one of them behind a blue slip sheet?

A. It's DTX-717?

Q. Yes, 717.

A. Yes, it's there.

THE COURT: I'm sorry, how many are we supposed to

have behind the blue sheet, just one?

MR. BEST: There should just be one document.

THE COURT: Yes, there is.

MR. BEST: And I think it is the English translation that was marked yesterday as DTX-2052.

BY MR. BEST:

Q. So, do you recall testifying about this document yesterday?

A. Yes.

Q. Now, looking at either version of this that you're more comfortable with, would you just confirm for me that the only cis-trans isomeric pair that was separated and evaluated in the context of this paper were the stereoisomers of tramadol?

A. Yeah, that's my recollection, yes. I think that's what's in the title and -- sorry. I just want to be sure.

Q. No problem. Many witnesses have had a lot of time in this case, so you should not be shortchanged.

A. I beg your pardon?

Q. Never mind.

A. Okay. I was looking through to see if there is anything about the metabolite, and I don't see anything, but so the conformational analysis was done on tramadol, yes, and the cis-trans forms of tramadol, not desmethyl.

Q. Correct. And none of the compositions discussed in Flick, with the exception of L201, which is the various

stereoisomers of tramadol, are discussed in this Frankus article, correct?

A. None of the which?

Q. So, aside from L201, which is discussed both in Flick and in this Frankus article, would you agree with me that none of the other compositions discussed in Flick are in the Frankus article?

A. Let me look at that one table where they --

Q. Sure.

A. He's got some other numbers here, the 280 -- 380. So, I don't know for sure, but my guess is that these numbers he has are new numbers that are associated with the cis isomer and the trans, optically pure trans minus and trans plus. So, I think what you said is correct. I don't think any of these numbers correspond to numbers in Flick.

Q. Other than L201?

A. I'm sorry, yes, other than L201. L -- E265, I don't think that was in Flick either.

Q. And as a consequence, Frankus only reports data for cyclic backbone compounds, correct?

A. That's correct.

MR. BEST: Now, could we go back to the Flick article at 715 for the screen?

BY MR. BEST:

Q. Probably you will want the English which I think has

been marked DX-108 in your binder.

A. Yes, it has.

Q. Now, you understand that this paper was published in 1978, right?

A. Correct.

Q. Now, would you agree with me that Flick and his colleagues only examined something like 30, maybe 25, maybe 28, but something like 30 different analogues of tramadol?

A. Well, should we count them or -- I mean, there is -- that's probably on that order. I mean, it's, basically I think the compounds in Table 2 probably is all of them, and the number is probably similar to what you are suggesting. Without counting them, I don't know exactly, but I think that's a fair representation.

Q. Now, nowhere does the Flick article discuss either analgesic or toxicity data for linear compounds; isn't that correct?

A. That's correct.

MR. BEST: And, in fact, if we go to page -- actually, Rob, could we have DX-108 in this instance on the screen, the English, not DTX, DX? It will be page 12, but not DTX, DX. Maybe I'll just have to put it up if you don't have it. A pause for reflection.

MR. CAPUANO: I think it is DTX-834 as well.

MR. BEST: Yes, let's try DTX-834. Maybe it will

be good enough to read. And could we go to page 12?

BY MR. BEST:

Q. Now, would you agree with me that the Flick article notes specifically that the basic structure of compounds with analgesic activity must possess a cycloalkane structure?

A. Can we highlight what you are referring to, sir?

Q. Absolutely.

MR. BEST: Could we highlight note 1 and blow it up?

BY MR. BEST:

Q. Would you read actually what note 1 says into the record.

A. Right. "The basic structure of the compounds with analgesic activity must consist of a cyclohexane radical substituted with phenyl in 1 position connected in 2 position to a basic amino group over a methylene bridge." And I think that -- well, with the sort of Raffa paper before, this one, any paper really, we have to -- the results and conclusions of any paper have to be put in the context of what that particular study was and what it included. And so this particular study was largely, as you pointed out, studies of cyclohexanols. Right? There's only one example of I think a five-membered ring and one of a seven-membered ring.

So, based on those results, he's saying that in this particular class of compounds, you have to have a six-membered

ring, a five-membered ring isn't good and a seven-membered ring isn't good. So, you have to read this comment within the context of the article.

Q. Well, would you agree with me then that this article does not provide context for making linear analogues of the basic tramadol core structure since no such compounds were evaluated in this article?

A. I've said that several times already, yes, it doesn't provide guidance for that, no.

Q. Now, I just wanted to correct you. I think you read the word "cyclohexane" when you read this into the record, but would you agree with me that it reads cycloalkane?

A. I'm sorry, cycloalkane, yes. Oh, okay. But let me step back, still within the context of this work, yes, I did misread it, but it's cycloalkane, still in the context of this work, it's the cycloalkane radical, so I'm not quite sure what this conclusion means because all of his compounds, I don't know that there's a single structure in that table that diverts from this description. I'd have to go look, but I think all of them fit this rule.

Q. Well, the author says here, "The basic structure of the compounds with analgesic activity must consist of a cycloalkane radical." Correct?

A. Right. Again, based on this study. He's well aware that morphine has this activity. So, when we're talking about

these cycloalkanols, right, and that's all this paper is about. The title I think was -- did it say? It says cyclohexanols. So, all we know from this paper is the context of this paper and the conclusion is based on all the studies that are presented in this paper. So, what I'm saying is that all of his compounds have -- fit this rule number 1. So, this isn't really an enlightening conclusion. That's all I'm saying. It doesn't -- it doesn't tell us anything really.

Q. You've relied on other conclusions in this paper, though, correct?

A. Yeah, some of them make -- are more conclusory than this one is, though.

Q. Could we, while we're here, could we look at -- actually, rather than looking, you testified that a person of ordinary skill would have been motivated to remove the phenolic methyl group in developing a new analgesic starting with the new tramadol compounds, correct?

A. Yes.

Q. And you have based that opinion on comparative data shown in the Flick article suggesting that the O-desmethyl composition had higher analgesia than the O-methyl, correct?

A. Well, not solely on Flick. Hennies also did this, this assay, and as far as I understand with Hennies, he looked at pure compounds, not mixtures of diastereomers, and he also pointed out that O-desmethyl was about threefold more active

than tramadol.

Q. Now, the Flick article was published in '78, which I think we talked about before, correct?

A. Yes.

Q. And the Hennies article, which if you want to look at it --

A. '81 or something. I don't remember.

Q. I think '88.

A. Okay.

Q. If you look at DTX-691. Is that the article to which you have been referring as Hennies?

A. You said DTX?

Q. 691.

A. Okay. Hang on. Right. That says '88.

Q. Now, you would agree then that both of --

A. Do I need to keep this?

Q. No. I just wanted you to have the date in mind. Now, you would agree that both the Flick data, 1978, and the Hennies data, 1988, were available to a person of ordinary skill in the art as of their publication dates, right?

A. Yes.

Q. Now, a person of ordinary skill would also know that Grunenthal did not develop O-desmethyltramadol as an analgesic at any point, correct?

A. Well, I don't know what they did with it. They never

got to the market. So, I don't know what they did about looking into it. I have no idea.

MR. BEST: Could we look at slide number 53 of your presentation? Go back one. I'm sorry. Forward one maybe. This is it.

BY MR. BEST:

Q. So, when you were talking about this slide earlier, I just want to confirm to you this second bullet point. And it reads, "It would be obvious to a POSITA to use an improved analgesic to treat pain." Do you see that?

A. Yes.

Q. Was the improved analgesic you had in mind tapentadol?

A. In this particular instance, yes. This is what this is all about.

Q. Now, would you agree with me that the effect on bioavailability of converting a meta methoxy group of the tramadol molecules to the O-desmethyl equivalent could not be determined a priori, that is, before running the experiment?

A. Sure.

Q. And would you say the same of the effect on bioavailability of other similar modifications to the tramadol core structure?

A. So, when we're doing bioavailability, let me understand what the experiment is. The experiment is we dose animals and we look at plasma concentrations and things of this sort?

Q. Sure.

A. So, now, could you repeat your question, please?

Q. Sure. So, would you agree with me that a person of ordinary skill -- in general, the effect on bioavailability of chemical modifications would have to be measured; it could not be predicted a priori?

A. It is a very difficult thing to predict.

Q. The same is true with toxicity, correct?

A. Yes, these are all things that are very important in drug -- I use that word very important -- in drug discovery, you have to worry about these things, yes.

MR. CAPUANO: Your Honor, let me just object that we're getting into now bioavailability, pharmacology and clinical science. That is beyond the scope of what Dr. Martin is here for.

MR. BEST: So, I will represent that these questions were asked of Dr. Martin in his deposition and he responded the same as this, and I'm done with that line in any event.

MR. CAPUANO: Okay.

MR. BEST: So, I have a document that I'd like to introduce that I think is not in your binders.

May I approach, your Honor?

THE COURT: Yes.

MR. BEST: Now, for identification purposes, we

have marked this as PTX-3000.

MR. SCHULER: For Roxane Laboratories, we just note that the pretrial order I think notes that additional exhibits are for purposes of either impeachment or refreshing memory, and I don't see a predicate for either right now.

MR. BEST: The predicate will become clear upon the first set of questions, which relates to Dr. Martin's prior testimony this morning on naloxone.

THE COURT: So, is it, in fact, impeachment then?

MR. BEST: Correct.

THE COURT: All right. Any objection to the document?

MR. CAPUANO: No, happy to have it.

THE COURT: Happy to have it, okay.

(PLAINTIFF EXHIBIT PTX-3000 WAS RECEIVED IN EVIDENCE.)

THE WITNESS: Do I have a copy of this?

MR. BEST: Were you handed one? If not, I can get you one. You don't have it in the binder.

THE COURT: Do we have an extra one?

THE WITNESS: You didn't hand me one.

MR. BEST: We have an extra one.

THE COURT: Either way. Thank you.

THE WITNESS: Thank you.

BY MR. BEST:

Q. I'll give you a moment to look at this, but for

context, this morning I believe very early on you discussed naloxone, and I think you discussed it as an antagonist and that you thought it did not have analgesic activity. Do you recall that?

A. I don't know whether I said I didn't think or I wasn't sure, I don't know, but I characterized it as an antagonist, not an agonist, which is normally what you look for. So, it looks like I was right on the antagonist part, but I think you're going to tell me I'm wrong on the analgesic part.

Q. That's a fair guess.

A. Because I just read the paragraph. So, I stand corrected, I guess.

Q. No problem. Would you read the first sentence of this paper into the record, which has been marked PTX-3000.

A. The first sentence?

Q. Please.

A. "In a model of experimental pain in the rat, namely Freund's adjuvant-induced arthritis, we have previously shown that there is a dose-dependent bidirectional effect of systemic injection of the opiate antagonist naloxone: hyperalgesia is found with a high dose, 100 micrograms per kilogram IV, analgesia with lower doses, 10 to 300 micrograms per kilogram IV. Under different conditions, other authors have also demonstrated analgesic effects with relatively low doses of naloxone."

Q. So, the article, it's fair to say, discusses the fact that naloxone is, in fact, analgesic, correct?

A. Right. If I may read the next sentence, it is paradoxical they say. So, yes, I agree with what you're saying, but it...

Q. And if I could ask you -- we discussed earlier this notion of animal experiments with regard to such compounds.

MR. BEST: And if you could look -- if we could put up the next to last page of the paper.

THE WITNESS: The same paper?

MR. BEST: Same paper, penultimate page. And could we blow up right here?

BY MR. BEST:

Q. Do you see on the right, in fact, the penultimate sentence of the paper, which starts "as described above," do you see that?

A. As described above, yes.

Q. Would you please read that sentence into the record.

A. Sure. "As described above, an analogous biphasic naloxone effect has been reported in clinical pain in humans."

Q. And so is it fair to say that the authors are reporting that the effect that they saw in this animal model is also observed in humans?

A. Yes, it is.

Q. You can set this aside.

A. I beg your pardon?
Q. You can set this aside.
A. Okay.
MR. BEST: We have one more document to introduce, your Honor, for impeachment.
THE COURT: Okay.
MR. BEST: This one has been marked PTX-3001.
THE COURT: Any issue with this document?
MR. CAPUANO: Not yet, your Honor. We'll see where he goes.
THE COURT: Okay.
BY MR. BEST:
Q. Now, you discussed yesterday your contention that tramadol was unique with respect to certain characteristics. Do you recall that testimony?
A. Yes, I do.
Q. And I think you said that aside from tramadol, there is nothing else out there that had dual activity for analgesia; is that right?
A. I think I said I was not aware of anything.
Q. That's fair. So, let's look at this article by Foote, et al, published in 1988. And we can just focus on the summary.
MR. BEST: Blow up the whole summary, but I'd like to highlight the last sentence.

BY MR. BEST:

Q. Would you read the last sentence of the summary into it record.

A. Yes. "The coexistence of D1 dopaminergic and atypical opioid agonist properties represents a unique pharmacodynamic combination which is not shared with any other analgesic, and may provide safe and innovative pain therapy."

Q. So, would you agree that this compound is being described as atypical and is unique?

A. It is. Is this compound a -- has it been approved as a drug and shown to be safe and efficacious? I don't know what this compound is.

Q. Well, Dr. Martin, I think you testified this morning that FDA approval was not a requisite for starting material, correct?

A. Oh, I don't think I said that. I said that -- I said that it was -- I said this was not -- your compound, this compound, tramadol, was not FDA approved at that time. I did say that, but I said it was also approved in the -- in Europe and had been used and approved for years and shown to be safe and efficacious. I don't think I ever said or certainly never meant to suggest that FDA approval was a prerequisite, but -- and so my question here wasn't -- I don't remember what -- the record can show whether I said FDA, but more generally what I thought I said was is this approved as a drug somewhere and was

it shown to be useful and efficacious.

Q. And is it fair to say that it's your point of view that the starting point for developing a new analgesic in 1994 for a person of ordinary skill had to be a drug that had been administered to humans and proven on its own to be safe and efficacious?

A. I think, yes, I think that's a position I've maintained from the very beginning. We've discussed that in my deposition, and I said certainly -- I mean, one has to have -- a person of ordinary skill has to have some way of filtering all of the information that's out there. And so a good starting point in terms of thinking about possible leads are compounds that have already been shown to be safe and efficacious in whatever -- for whatever indication you are interested in. This to me doesn't look like -- I mean, again, that's why I asked you the question, is this compound an approved drug anywhere?

Q. I can't answer questions, Dr. Martin. You have to do that.

A. I'm sorry -- well, but that's my question, and if it isn't, then I would say this may be a unique compound and have unique properties like this in the sense that it acts on the dopaminergic system, which is a different one.

Q. And the opioid system, correct?

A. I'm sorry, and the opioid, and it has certainly been

characterized as atypical and unique, and I said I was unaware of this earlier when you asked me the question. But then again, I would circle back, and I can't ask you the question here, but I would, if I were looking at this, I would have not have considered this, whatever this compound is, and I don't know what it is yet, would not have considered it to be a possible lead. As I said at the very -- well, I don't remember whether I said it in this testimony or not. A lot of words have been said. But I think I made very clear at the beginning that a compound had to be an approved drug that had been shown safe and efficacious.

Q. I think you testified not two minutes ago that the compound did not have to be an approved drug to be a starting -- a reasonable starting point for a person of ordinary skill, correct?

A. I don't remember that testimony. That it did not have to be an approved drug?

Q. Correct.

A. You know, if you say to me, well, O-desmethyltramadol was not an approved drug and you want to connect those dots, I would have to agree with you, I suppose, but...

Q. I'm doing no dot connecting. I'm simply reflecting on your testimony. And going back to that testimony, isn't it fair to say that this compound has been described as both atypical and unique and the authors hypothesize it may provide

a safe and effective pain therapy, correct?

A. That's what it says.

Q. And would you agree with me that one of the goals that a person of ordinary skill had in 1994 in developing a new analgesic would be to minimize addiction potential?

A. That would certainly be one goal.

MR. BEST: Can we go to what internally is marked page 150? It would probably be the third from the last page in your PDF. And could we get this part and highlight "we therefore propose," that sentence?

BY MR. BEST:

Q. Now, would you agree -- well, first off, would you read this sentence into the record, please.

A. "We therefore propose that since CY 208-243 had no effect on dopamine metabolism, that it may lack the biochemical basis for addiction potential."

Q. Now, would you agree that all else equal, the lack of addiction potential would have motivated a person of ordinary skill to select this compound as a starting point as a new analgesic in 1994?

A. Well, it doesn't fit the other criteria of being an approved drug, but yes, in terms of the addiction potential, that was one of the advantages I discussed I think at the beginning of having this dual pharmacology, is that you are likely to have less addiction potential. And certainly for

tramadol itself, it was well known at the time anyway that it came out, that it had lower addiction potential anyway than a lot of the opioids. I think it's been changed since then, but certainly at this time it was viewed as being pretty good because it didn't have those addictive properties that the classic opioids did.

Q. Now, would you agree that on the basis of having read this article now --

A. I haven't read the article.

Q. Having skimmed the article. If you want a little more time to do so, by all means take it.

THE COURT: We can give you time to read it.

THE WITNESS: Let me just respond to your questions and I'll read it as needed.

BY MR. BEST:

Q. Sure. So, would you agree that you were not correct that there were no dual opioid and non-opioid analgesics known to the art in 1984 other than tramadol?

A. I would agree that that wasn't correct, but it was -- I think I'm probably correct and I'm quite sure I'm correct in saying there were no approved drugs other than tramadol that had this dual mode of action.

Q. And, in fact, you would agree that there might be other such compounds that had been known in the art at that time, correct, having these dual --

A. Well, you have shown me one. I wouldn't be surprised if you had another one. I don't know.

MR. BEST: I don't have any more questions at this time.

THE COURT: Thank you very much. All right. Do we have redirect?

MR. CAPUANO: Just very briefly, your Honor.

THE COURT: Yes.

MR. CAPUANO: May I have Mr. Best's demonstrative Exhibit Number 4?

That's number 3, I think. Yes.

(REDIRECT EXAMINATION OF DR. MARTIN BY MR. CAPUANO:)

Q. Professor Martin, do you remember Mr. Best asking you about Nazarov, one compound XIV that's shown on the right-hand side of this slide?

A. Yes, I do.

Q. And he seemed to suggest -- did he seem to suggest that because this compound has the hydroxyl group on the bridge-carbon esterified, that one might want to do that to (S,S)-O-desmethyltramadol?

MR. BEST: Objection, your Honor. Leading.

THE WITNESS: Actually, I don't --

THE COURT: Hold on one second. You can rephrase it, Mr. Capuano.

BY MR. CAPUANO:

Q. Do you remember Mr. Best suggesting to you that one might want to esterify (S,S)-O-desmethyltramadol?

A. You know, I don't know if -- honestly, I can't tell you whether -- he said that I was certainly expecting that to come. It seemed that if we connect these two things, it seemed -- it was logical for me to assume or think that because this compound on the right has this ester, that we might talk about the compound on the left having an ester.

MR. CAPUANO: Could I have my demonstrative Exhibit Number 27?

BY MR. CAPUANO:

Q. Do you remember looking at this in your direct examination, Professor Martin? This is from Flick Table 4.

A. Yes.

Q. And what does Flick Table 4 tell you about esterifying that hydroxyl position on cycloalkanol analgesics?

A. He clearly teaches away from it. The data he presents -- what's going on?

Q. I'm sorry. Stay there.

A. The data he presents for it's L205 and L204 show that these compounds were that bridge hydroxyl group has, in fact, been esterified with at least two different esters, that they're in one case -- well, in one case there was no analgesic activity up to the limit they tested. In the other case, it looks like there may have been some slight analgesic activity

at the maximum dose they tested.

Q. Exhibit DTX-733. Do you remember Mr. Best asking you about this paper from Raffa 2, what we've been calling Raffa 2?

A. I do.

MR. CAPUANO: Can you show the abstract?

BY MR. CAPUANO:

Q. Do you remember Mr. Best asking you that I only asked you about the left-hand part of the abstract and he wanted to tell you about the right-hand side, and he mentioned Paul Harvey telling about the rest of the story; do you remember he wanted to show you the rest of the story?

A. I do.

Q. Do you remember you asking him to show you Table 2?

A. I asked -- I think I asked him are we going to look at Table 2. I remember saying the word "Table 2."

Q. Did he ever show you Table 2?

A. No, he didn't.

Q. Would you like to see Table 2 and explain --

A. And see the rest of the story?

Q. And tell the rest of the story, yes.

A. Sure.

MR. CAPUANO: Can you bring up Table 2, please? There it is at the top.

BY MR. CAPUANO:

Q. And do you remember Mr. Best asking you about synergy

among tramadol isomers?

A. Yes, he did, I remember.

Q. What does this table tell you about -- what does the data in this table tell you or tell a person of ordinary skill in the art about whether tramadol is synergistic, and what does it tell you in particular about whether tramadol is synergistic when administered orally?

A. So, yeah, so this is interesting. So, probably if we look at the table and we look at the first two entries where we have abdominal constriction in the hot plate test -- let me say that I am not a pharmacologist. I think I said in my deposition I really didn't understand this test that they used. In fact, I looked at the data and I still couldn't quite get my head around what they meant by synergy. So, I was simply willing to take their conclusion without digging into it. You know, if I really wanted to be thorough, I would dig into it, but I didn't do that.

But the point is if we look at the first two entries and we look to the synergy column, it says there's synergy. So, I'll accept the fact that there's synergy in those two cases. However, and to your point about the oral activity, and I think if one of ordinary skill is interested in making a drug, oral bioavailability is the key thing. You want them to be orally available. And the PO, after that, the mouse in line 3 where it's the tail flick test. So, the first two tests are

the two tests for analgesia, the abdominal constriction test and the hot plate test, and then there's another test called the tail flick test, and interestingly, when it is administered orally, it is characterized as having no synergistic effect.

Q. Well, let me just ask you, in the tests that are reported here, how many are reporting no synergy and how many are reporting synergy?

A. Okay. Let's focus on the ones that have beneficial analgesic effects. So, that would be all the way down to side effects. So, if we don't include the side effect count, there are four yeses and five nos.

Q. And in the one test where it was given orally, is synergy reported as yes or no? Not the last two.

A. No.

MR. CAPUANO: Let's have my demonstrative Exhibit Number 20.

BY MR. CAPUANO:

Q. Professor Martin, do you remember Mr. Best asking you whether you, in fact, identified a single compound as a starting point as a lead compound in your analysis?

A. I certainly identified a preferred starting point, yes.

Q. And is your preferred starting point shown on demonstrative Exhibit 20 as (S,S)-O-desmethyltramadol?

A. It is.

Q. Professor Martin, are you aware of any information that

compares tapentadol with the same compound lacking the hydroxy group on the aromatic ring?

A. Okay. Your question is comparing the tapentadol itself with the compound lacking the hydroxy group on the aromatic ring?

Q. Yes. And I strike the question because it was my fault.

Are you aware of any information or data that compares tapentadol with the same compound that also has a hydroxyl on the bridge-carbon?

A. It seems -- I can't remember for sure. That may have been one of the examples in the '593 patent. I don't remember. There were some examples in the '593 patent in that -- the bioactivity. So, I don't know if that's -- I don't remember if that's one of them. There were several in there that -- I think that compound may have been in there, but I don't remember for sure.

MR. CAPUANO: Okay. Let's have my demonstrative 756 that Mr. Best used.

Can we put it up using your PowerPoint?

MR. BEST: Yes, of course. I think the problem is that our electronic version is not the version you printed off for us.

MR. CAPUANO: Let me show it at the ELMO. You got it. Thank you.

BY MR. CAPUANO:

Q. Do you remember Mr. Best asking you about this slide?

A. I do.

Q. And does tapentadol have the OH that's at the top of structures A, B and C?

A. So, are you asking me does tapentadol have this -- if we look at this structure here, let's say, an OH here?

Q. Tapentadol doesn't have this OH --

A. I'm sorry. Okay. I wasn't looking at that. No, it does not have that OH.

Q. And that's the OH at the top of structures A, B and C?

A. That's correct.

Q. And that's the one he was asking you about, about hydrogen bonding, correct?

A. That's correct.

Q. OH doesn't exist in tapentadol?

A. It does not exist in tapentadol, no.

MR. CAPUANO: Thank you. I have no further questions, your Honor.

THE COURT: Thank you. Anything further?

MR. BEST: I have nothing further, nothing.

THE COURT: Anything from anyone?

MR. CAPUANO: I might have something.

THE COURT: Okay.

MR. BEST: Maybe I will have some.

MR. CAPUANO: No further questions, your Honor.

THE COURT: All right. Thank you very much. You are released as a witness. Thank you for your testimony today.

THE WITNESS: Thank you.

THE COURT: We do appreciate it. All right. You may step down. Just be careful of the step. Thank you.

(Witness excused.)

THE COURT: I think this is a good time to break for lunch. All right? So, we'll see you back here in 45 minutes. Thank you.

THE DEPUTY COURT CLERK: All rise.

(Recess at 12:45 p.m.)

(In open court at 1:37 p.m.)

THE DEPUTY COURT CLERK: All rise.

THE COURT: Hello, everyone. Have a seat. Folks, we are on with the next witness. Mr. Aly?

MR. ALY: Your Honor, before we call the next witness, I just wanted to advise your Honor what I advised plaintiffs during the lunch break, that is, because Dr. Martin's testimony was long and covered the subjects that Dr. Prisinzano was going to cover, we'll withdraw Dr. Prisinzano, and that will be offered on behalf of all the defendants, the testimony that Dr. Martin has given. Bottom line is one more witness for today and this week, which is the next witness, Dr. Wolf.

THE COURT: All right. That sounds fine. How long do we think this witness will go for?

MR. SOBOLSKI: Approximately an hour, your Honor.

THE COURT: An hour? And then?

MR. GLANDORF: Half hour, 45 minutes of cross.

THE COURT: All right. That's fine. Sounds good. Then I guess, going back to where we were yesterday, so assuming that, then we would not sit tomorrow and we would resume on Monday, and we would resume on Monday with, who is it at this point?

MR. ALY: We have a witness, who will be Dr. Buvanendran, on the '130 patent. Of course, that's weather permitting.

THE COURT: I just looked at my forecast for home, which is three to six inches, which I don't understand, but we'll see how it goes. I have a feeling it's going to be less than what is predicted, but if it is actually something, as I indicated, we'll contact Mr. Miller, let him know what's happening with the court, because sometimes they do a delayed opening if the roads are slick. So, I'll let you know how that works out, because he has everyone's e-mail and we'll be able to contact you. So, hopefully it's nothing, but in case, you have the whole procedure set up for what happens. Thank you. Right?

Anything else we have to deal with in terms of our

schedule? Anything else?

MR. ALY: Not that I know of.

THE COURT: Okay. So, let's start with the witness.

MR. SOBOLSKI: The defense calls Dr. Christian Wolf, your Honor.

THE COURT: Thank you.

MR. SOBOLSKI: Your Honor, we have a witness binder and demonstratives, if we may approach.

THE COURT: Certainly. You may exchange them. We'll have the witness sworn in.

(**CHRISTIAN WOLF, Ph.D.,** HAVING BEEN DULY SWORN, TESTIFIED AS FOLLOWS:)

THE DEPUTY COURT CLERK: You can step up and state your name for the record.

THE WITNESS: Christian Wolf.

THE COURT: Thank you. Good afternoon, sir. How are you?

THE WITNESS: Good. How are you?

THE COURT: Good. Thank you.

Let's begin. Thank you.

MR. SOBOLSKI: Thank you, your Honor.

(DIRECT EXAMINATION OF CHRISTIAN WOLF BY MR. SOBOLSKI:)

Q. Good afternoon, Dr. Wolf. Please state your name for the record.

A. Christian Wolf. Good afternoon.

Q. Dr. Wolf, have you prepared demonstratives in connection with your testimony today?

THE COURT: You know what, let me just stop you. I'm sorry. Was there any issue with respect to the exhibits or the demonstratives?

MR. GLANDORF: No objection.

THE COURT: Thank you. Go right ahead.

MR. SOBOLSKI: Thank you, your Honor.

THE WITNESS: Yes, I did.

BY MR. SOBOLSKI:

Q. And are these the demonstratives you prepared in connection with your testimony today, Dr. Wolf?

A. Yes. I prepared a few slides with regard to my professional qualifications, the scientific background that I think is important for the discussion of this patent, and a few other opinions about the patent as well.

Q. Thank you, Dr. Wolf. Let's begin with your professional qualifications. Please start by telling the Court your current professional affiliation.

A. I am professor of chemistry at Georgetown University. I've been there since 2000. I run a research group with about seven or eight graduate students, typically sometimes a post-doc and a few undergrad students, and we are interested in developing organic chemical synthesis. We are working on the

making and analysis of chiral compounds, stereochemistry in general. We are also interested in chiral cognition, chemosensing projects, drug discovery and so on.

Q. And in addition to your laboratory research, Dr. Wolf, do you also teach students at Georgetown?

A. Yes, I typically teach a course each semester in the areas of organic chemistry, stereochemistry, and synthetic methods, both on the undergraduate and graduate levels.

Q. Thank you, Dr. Wolf. Please tell the Court about your scientific training in the field of organic chemistry and stereochemistry.

A. I obtained a Ph.D. in chemistry from the University of Hamburg in 1995, working on the synthesis and analysis of chiral compounds, and then I was further deepening my expertise in this area as a postdoctoral fellow at the University of Illinois from 1996 to 1997, and I obtained my first job as a scientist at SmithKline Beecham Pharmaceuticals in 1997 and stayed there until 2000, and I was working there at the development of drug candidates and pharmaceutical compounds.

Q. And during your time at SmithKline, Dr. Wolf, were you developing optically active drug candidates?

A. Yes, I did.

Q. Dr. Wolf, has your scientific work in the field of stereochemistry been published?

A. Yes. I have published over 100 papers, a few book

chapters and a textbook on stereochemistry. Most of these publications deal with the making and analysis of chiral compounds. I am also frequently working as a peer reviewer for about 20 international journals. I have several collaborations with the pharmaceutical industry and academic partners as well.

Q. And has your work in the field of stereochemistry been recognized, Dr. Wolf?

A. Yes. I am an editorial board member of the journal called Chirality, and I have received a few awards I've listed here.

MR. SOBOLSKI: At this time, your Honor, defendants would like to offer Dr. Wolf as an expert in organic chemistry, including stereochemistry and the synthesis, analysis and characterization of optically active compounds.

THE COURT: Thank you. Any objection?

MR. GLANDORF: No objection.

THE COURT: Thank you. He is so admitted as an expert in those areas. Thank you.

MR. SOBOLSKI: Thank you, your Honor.

BY MR. SOBOLSKI:

Q. Dr. Wolf, what is organic chemical synthesis?

A. I prepared a slide here that explains the basics of organic chemical synthesis, which is about the making of organic compounds. So, as scientists, we typically start with an idea to make a compound, and then we select starting

materials for this, and think about a reaction, certain reaction conditions, which could be reaction time and reaction temperature, and then one way to characterize reaction and organic synthesis would be, for instance, to look at the yield, and that is defined as the amount of product compared to the theoretical amount that one could make, as shown in this equation, but then the very important question that we have to ask ourselves is obviously did we actually make the compound that we anticipated to make. So, did we make that hypothetical compound as we thought we would?

So, there are a number of steps that we then do. It starts typically with the product isolation, and so techniques that I use to isolate products are, for instance, chromatography, crystallization and extraction, and then once we have the isolated purified compound, we try to identify the structure. And techniques that I use to do that is, comprise NMR spectroscopy, mass spectometry, crystallography and combustion analysis. And then we run some tests to further characterize the product, and those could be including melting point range determinations and optical rotational analysis.

Q. And for the record, this was demonstrative 8.

Dr. Wolf, explain for the Court, please, what is an isomer?

A. I show this on this slide here. Isomers can be either constitutional isomers, which are compounds with the same

structural formula, but different atom connectivity. And then we have another class which are stereoisomers. These have the same atom connectivity but different spatial orientation of groups and atoms. And so in this class we have two classes, one is the class of enantiomers, which are defined as non-superimposable mirror images, and all other stereoisomers that are not enantiomers are diastereomers.

Q. Dr. Wolf, you testified about enantiomers. How are enantiomers described in organic chemical literature?

A. So, I'm showing on this slide, for an example, it's an illustration of two non-superimposable mirror images. The blue line, the blue vertical line that you see there would be the mirror. So, these are non-superimposable mirror images. The one on the left side, we could mention as the R enantiomer, and the one on the left is the S enantiomer. These are chiral compounds. They have a chiral center, and the word "chirality" comes from Greek and it basically means handedness. So, we can kind of think of these hands there, the right hand and the left hand, to refer to the chirality. So, these labels are very important. They refer to fundamental aspects of stereoisomerism in chiral compounds.

So, even though these two mirror images look like they're almost identical, they are sometimes having very different chemical and biological properties, and that can be like a night and day comparison.

One example is, for instance, the example of thalidomide. Thalidomide was also known or is also known as Contergan. That is a drug that was used to treat pregnant women in the '60s in some European countries. We know that the R enantiomer treats nausea and morning sickness whereas the S enantiomer causes severe birth defects. So, you see how different they can be in terms of their biological activities.

And you can think of this as the example of the right hand fits into the right glove and the left hand fits into the left glove. So, human beings are also made of chiral compounds. And so some enzymes, some receptors might have just the right glove, so the R enantiomer fits in, has a certain function, the S enantiomer might not fit in or might not fit in as well. So, you can see they might act at different places in the human body or they might act differently. And so that's why we get to these, in some cases, night and day differences between enantiomers.

Q. For the record, this is demonstrative 10 citing DTX-1574. Let's turn to demonstrative 11, Dr. Wolf. What, if any, are pertinent properties of isomers?

A. So, there's more to the stereo descriptors, as I just mentioned. For instance, chemists would know, a person of ordinary skill in the art would know that enantiomers have the same melting point ranges and opposite optical rotation that's inherent properties of enantiomers, whereas diastereomers

typically have different melting point ranges and different optical rotations.

Q. And what is the import of those properties, Dr. Wolf?

A. It tells us a lot. If you have different melting point ranges, we know we are not looking at enantiomers.

Q. Thank you, Dr. Wolf. Let's turn to demonstrative 12 where you presented your analysis of U.S. patent RE39,593, and let's turn to demonstrative 13. Is this, in fact, the patent that you have analyzed in connection with your testimony today, Dr. Wolf?

A. Yes. This is a part from the cover page of the '593 patent, which I understand is a reissued patent, so I've also looked at the parent patents.

Q. And which claims have you analyzed in connection with your testimony today, Dr. Wolf?

A. I think that's on the next slide.

Q. And this is demonstrative 14?

A. Yes.

Q. What are those claims, Dr. Wolf?

A. These are the claims I've looked at for my testimony today, which are claim 8, 61, 117 and 147.

Q. Let's turn to demonstrative 15. Dr. Wolf, do you understand that the Court has construed one of the claim limitations that appears in claim 61 and 117?

A. I'm aware of that.

Q. And did you consider that construction in connection with your testimony?

A. Yes. I have used this construction for my analysis today.

Q. Let's turn to demonstrative 16 where you have presented a definition of person of ordinary skill in the art. Why have you done so, Dr. Wolf?

A. Yes. My understanding is this is the definition of the defendants, and I think it's a very reasonable definition for a POSITA, what myself in industry and academia as a team member in such efforts.

Q. And did you consider this definition of a person of ordinary skill in the art in connection with your testimony today?

A. Yes, I did.

Q. Let's turn to demonstrative 17 where you presented plaintiffs' proposal of a person of ordinary skill in the art. Did you consider this definition, Dr. Wolf?

A. Yes. I find it to be very similar, and the opinions that I have today are independent of which definition one would choose.

Q. Thank you, Dr. Wolf. Let's turn to demonstrative 18 where you have presented the four asserted claims in the '593 patent. Does this present your conclusions?

A. Yes. I have some conclusions for claims 8, 61, 117 and

147, and I also have some opinions related to some of the aspects that Dr. Mogil testified a few days ago.

Q. And those opinions that you referred to from Dr. Mogil, have you read the transcript of Dr. Mogil's testimony in this case?

A. Yes, I did.

Q. Let's turn to demonstrative 19 where you have indicated your opinions in relation to the lack of utility of claims 8, 61, 117 and 147. In connection with your review of Dr. Mogil's testimony, Dr. Wolf, did you find any further pertinent information?

A. So, I know that Dr. Mogil looked at this table here from the '593 patent, and I agree with him that there is no information on Example 25 in this table. So, as a chemist, my conclusion is a person of ordinary skill in the art would not know anything about any activity of Example 25. The fact that there is Example 24, which is the purported enantiomer of 25, also wouldn't tell us anything about the activity of 25.

Q. And why is that, Dr. Wolf?

A. It's the other purported enantiomer and, as I just explained with the example of thalidomide, they can have drastically differently biological activities, so one wouldn't know.

Q. And for the record, this is an excerpt from column 22 of the '593 patent on demonstrative 20. Let's turn to

demonstrative 21, Dr. Wolf. Did you find any other information meaningful in connection with the table of the '593 patent?

A. Yes. What I have highlighted here in the red rectangle is that there are a number of entries about racemic compounds, and the racemic compound is a mixture of both enantiomers in a 1 to 1 ratio. So, looking at this again, one wouldn't know about the individual activities of enantiomers that were a part of this mixture.

Q. Thank you, Dr. Wolf. Let's turn now to demonstrative 22 in which you have introduced your obviousness analysis in connection with claims 8, 61, 117 and 147. Let's start on demonstrative 23. What standard were you asked to apply in connection with your obviousness analysis?

A. I have listed here the factors that I was asked to apply into this analysis, and I also understand that a POSITA must be motivated and must have a reasonable expectation of success to follow that motivation.

Q. Now, on demonstrative 23, Dr. Wolf, you have indicated as one factor the scope and content of the prior art. What was the date that you used to assess the scope and content of the prior art?

A. Based on Dr. Mogil's opinion that the earliest date for possible utility would have been in 2005, I looked for prior art before 2005 and I found an interesting article there about tapentadol.

Q. Okay. And let's turn to demonstrative 24. Is this the prior art about the tapentadol about which you just testified, Dr. Wolf?

A. Yes. This is a document from the World Health Organization titled World Health Organization Drug Information that was published in 2002, and if you look there at the bottom, it says international nonproprietary names for pharmaceutical substances. So, this is for pharmaceuticals; it's not just a catalog of chemicals. It's about pharmaceuticals. And what we see here is the name and the structure of tapentadol, and it says it's an analgesic.

Q. For the record, this is an excerpt at page 184 of DTX-260.

Let's turn to demonstrative 25, Dr. Wolf, starting with your analysis of claim 8 of the '593 patent.

MR. SOBOLSKI: Let's return for a moment to demonstrative 23, please, Mr. Haw.

BY MR. SOBOLSKI:

Q. Now, in connection with your analysis of claim 8 of the '593 patent, Dr. Wolf, what, if any, differences between the prior art World Health Organization reference and claim 8 would a person of ordinary skill in the art observe?

A. I don't think there is any difference.

Q. Turn back to demonstrative 25, please.

A. So, I think the person of ordinary skill in the art

would find the claim obvious with regard to the document from the World Health Organization. It is about a method of treating a mammal suffering from pain, and the document from the World Health Organization says this is an analgesic. So, it discloses tapentadol as an analgesic.

Q. And why would that be -- why would the disclosure of tapentadol as an analgesic be significant to a person of ordinary skill in the art?

A. A person of ordinary skill in the art would understand that the WHO document talks about pharmaceuticals that would be used for the treatment of mammals, in particular humans, so one would be highly motivated to use it for treating mammals suffering from pain.

Q. And in that motivation, would a person of ordinary skill in the art have a reasonable expectation of success in treating that mammal suffering from pain based on the disclosure of the World Health Organization reference?

A. Yes, because it's labeled as an analgesic, and I think I have on another slide testimony from Dr. Friderichs, who is one of the named inventors, who I think basically says the same.

Q. And let's look at that testimony. Is this the testimony you have presented on demonstrative 26 from page 166 of Dr. Friderichs' deposition transcript?

A. Yes. And so Dr. Friderichs says this will be a

compound -- an analgesic would be a compound that alleviates pain. So, a person who wants to treat pain would have a reasonable expectation of success doing this with an analgesic.

Q. And let's return for a moment to demonstrative 25, Dr. Wolf, where you have presented the language of claim 8. Do you have an understanding of the compounds encompassed by claim 8, Dr. Wolf?

A. Yes. And I will discuss this in more detail a little bit later.

Q. And did you consider, Dr. Wolf, whether any of the compounds encompassed by claim 8 other than tapentadol appear in the 2002 World Health Organization reference at DTX-260?

A. Yes, I looked through the whole document and I couldn't find any other compound covered by this claim in this WHO document. So, tapentadol is the only one.

Q. Thank you, Dr. Wolf. Let's turn now to demonstrative 27 where you have presented further, a further excerpt from the deposition testimony of Dr. Friderichs. What have you identified here, Dr. Wolf?

A. Yes, so a person of ordinary skill in the art would know that the WHO document teaches to use tapentadol for treating pain. And so a POSITA could then confirm this with -- would be motivated to confirm it, would have a reasonable expectation of success confirming this, and just by doing this with a few animal tests within a few days.

Q. Thank you, Dr. Wolf. Let's turn to demonstrative 28. Did you analyze obviousness in connection with the limitations of claim 61, 117 and 147?

A. Yes, I did.

Q. And let's begin with the limitations you have identified in claim 61 and 117. Will you identify for the Court what that limitation is?

A. So, in claim 61 and 117 there is mention of a hydrochloride.

Q. And what is the limitation you have identified in claim 147?

A. It's a pharmaceutically acceptable salt.

Q. What, if any, difference between the content of claim 61, 117 and 147, would a person of ordinary skill in the art identify in relation to the 2002 World Health Organization reference?

A. I think there is very little difference.

Q. Let's turn to demonstrative 29. Why do you believe a person of ordinary skill in the art would find very little difference between those three claims and the World Health Organization reference?

A. Because I think a person of ordinary skill in the art would be highly motivated to make a hydrochloride salt, a pharmaceutically acceptable salt of tapentadol. What I show you here is on the top an excerpt from the Gould publication

which is from 1986. It is called Salt Selection for Basic Drugs, so that's what we do for pharmaceuticals, and it mentions the formulation as hydrochloride have been by far the most frequent choices. So, it's about 40 percent, which is highlighted here in the green rectangle.

Q. For the record, that's DTX-1575, the Gould reference. Please go on, Dr. Wolf.

A. I also have mentioning here of the Berge reference in the second table. That's only an excerpt, actually, of that table. That's from 1977. And if you go towards the second entry from the bottom, you basically get the same message, the hydrochloride here was 43 percent compared to others. So, that would be, a person would be motivated to make a salt formation, in particular hydrochloride salt, from tapentadol.

Q. And Berge is DTX-176 at page 2.

A. And finally I have also a reference to Gennaro from 2000 which basically echoes the other two references.

Q. And Gennaro is DTX-1580. Thank you, Dr. Wolf.

Let's turn now, Dr. Wolf, to demonstrative 30 in which you have introduced your analysis of the lack of -- a final question in connection with demonstrative 29, Dr. Wolf. Would a person of ordinary skill in the art have a reasonable expectation of success in obtaining the hydrochloride salt of tapentadol?

A. Based on these references, yes.

Q. And would a person of ordinary skill in the art have a reasonable expectation of success in obtaining a pharmaceutically acceptable salt of tapentadol as disclosed in the World Health Organization reference from 2002?

A. Yes.

Q. Thank you, Dr. Wolf. Returning to your analysis of lack of written description, what is the legal standard you were asked to apply in connection with that analysis of claims 61, 117 and 147?

A. My understanding is that a person of ordinary skill in the art looking into the four corners of the specification would have to see that there is evidence that the inventors, indeed, invented what they claimed they had invented, and this, of course, would be an objective inquiry that would be contextual, and that means in the context of this exam, it would be about the making of a new -- of new chiral compounds.

Q. Thank you, Dr. Wolf. And let's turn to demonstrative 32 where you have excerpted the language of claims 61, 117 and 147. Are these, in fact, the claims you have analyzed?

A. That's correct. And I know that these are all about the 1R,2R stereoisomer.

Q. Let's turn to demonstrative 33, Dr. Wolf. You have presented here an excerpt from column 19, lines 11 to 30 of the '593 patent. What data, if any, what information, if any, would a person of ordinary skill in the art observe in the '593

patent in connection with your analysis of those claims?

A. So, this is where a POSITA would find information about Example 25, and the first thing a POSITA would notice is that there aren't any structural data here.

Q. What do you mean by there are no structural data presented in Example 25?

A. So, what you see here is a depiction of a hypothetical structure, and a name, which actually was changed from 1R,2S to 1R,2R, and a person of ordinary skill in the art would find information that this is an enantiomer that was obtaining 45 percent yield. And then there is a reference to Example 24, so one would understand there are enantiomers here discussed. The only data that I found here don't tell us anything about the structure. There's a melting point range of 168 to 170 degrees, and then there's a specific rotation which is -- which was determined as minus 27.5 degrees.

Q. Now, Dr. Wolf, by the mid 1990s, would structural data and structural tests have been known to a person of ordinary skill in the art?

A. Absolutely, and I think I have a slide on that as well.

Q. And let's turn to demonstrative 34. Is this the demonstrative you are referencing?

A. Yes. So, what I'm listing here is basically what I've said earlier. There are several techniques, and I just list a few of those, that were commonly used in the '90s that one

could use to elucidate a structure of the compound. That would be spectroscopy, for example, proton and carbon NMR spectroscopy, or IR, which stands for infrared spectroscopy, also x-ray crystallography, mass spectometry, and combustion analysis. None of these tests are in the '593 patent.

Q. Now, Dr. Wolf, what did the literature in chemistry say in regard to the use and presentation of structural data?

A. I have a few slides to that effect.

Q. Let's begin with demonstrative 35 where you have presented an excerpt from DTX-222 at page 8A, a 1993 reference.

A. This is from the Journal of Organic Chemistry in 1993. It is from the Guidelines for Authors. And what it says here is that for the -- in order to prove identity of new compounds, one should be considering proton and carbon NMR spectroscopy, infrared spectroscopy, and mass spectometry.

Q. Now, Dr. Wolf, in the excerpt you selected from DTX-222 that you just testified about the use of these data for "all new compounds," what is the significance, if any, of the term "all new compounds?"

A. Well, this is not a high standard that is required here, but if you think about a new compound, there is no reference framework. So that it is very important to get structural data for new compounds.

Q. Now, Dr. Wolf, DTX-222 is from the Journal of Organic Chemistry. Did you consider literature outside of the context

of academic journals in chemistry?

A. Yes. I think it's on the -- one of the next slides.

Q. Let's turn to demonstrative 36 where you have excerpted from the Sibilia reference at DTX-1581, page 2.

A. Yes, this is from 1988, and it brings me back to what I said earlier when I discussed organic chemical synthesis. The important question that we as chemists always ask ourselves when we have run a reaction, did we actually make what we hypothesized we would make? And so this is actually saying the same. And so in this case there is a suggestion to run infrared IR spectroscopy or magnetic NMR spectroscopy to identify the structure. And I like to note that this is also about, if you look in the second line, it's about pharmaceuticals.

Q. Thank you, Dr. Wolf. Now, you have been testifying about the use of structural data for new compounds. Did you consider any literature about the use of structural data in connection with known compounds?

A. Yes, I did. I think that's on the next slide.

Q. And this is demonstrative 37 where you have presented an excerpt from DTX-274. What is this reference, Dr. Wolf?

A. This is from a textbook that one could use for undergraduate teaching purposes. It is about the synthesis of aspirin, a known compound. And even in this situation, a chemist would verify the outcome of the reaction and do some

spectroscopy. So, in this case what is mentioned here is using UV spectroscopy to make sure that the compound that was expected to be formed is made.

So, the chemistry is an empirical art and it is not predictive. Even if you run reactions, there are in the literature where we know the starting materials, the conditions, we always check if the product that we wanted to make has actually been made. So, even for known compounds, not to mention new compounds.

Q. Thank you, Dr. Wolf. And did you consider any -- use structural data in the context of patents?

A. I did. I think that's on the next slide.

Q. And let's turn to that which is demonstrative 38. And you have an excerpt here from DTX-263, which is U.S. patent number 5,061,398 issued October 29, 1991. What is this patent, Dr. Wolf?

A. This patent is from 1991, and it's about an optically active compound. And so what the inventors provide in this patent is structural data in the form of mass spectroscopy and proton NMR.

Q. Thank you, Dr. Wolf. In your own work, you testified earlier that you have synthesized optically active compounds, correct?

A. Correct.

Q. When did you begin that work, Dr. Wolf?

A. In the 1990s.

Q. And what has your practice been in connection with presenting the results of your synthesis of new organic compounds?

A. So, my practice has been, when we discuss the synthesis of new chiral compounds, to provide structural data for these new compounds.

Q. Thank you, Dr. Wolf. Let's turn to demonstrative 39. You have included here again the excerpt from the '593 patent containing Example 25. What data would a person of ordinary skill in the art find disclosed under Example 25?

A. Well, what one does not find, to begin that way, is that there aren't any structural data. So, instead of data that tell us anything about the structure of Example 25, there is a melting point range and an optical rotation. These are important to characterize Example 25, but they don't tell us anything about the structure.

Q. And when you say -- and when you testify that these are important to characterize Example 25, what do you mean by that, Dr. Wolf?

A. Because, as I said earlier, we know that enantiomers must have the same melting point range. So, if they don't, if you have materials and they have different melting point ranges, we know they aren't enantiomers. So, it is going to be still useful information to have that.

Q. And Example 25 would be understood by a person of ordinary skill in the art to be an enantiomer of what, supposedly?

A. As I said earlier, you see here that enantiomer minus 21, in the sentence, was obtained in 45 percent yield under the conditions cited in Example 24. So, a person of ordinary skill in the art would then looking at that Example 24.

Q. And let's turn to Example 24. Let's turn to demonstrative 40, Dr. Wolf, in which you have excerpted Examples 24 in part and Example 25 of the '593 patent. What would a person of ordinary skill in the art conclude based on the information presented in connection with those two examples?

A. A person of ordinary skill in the art would observe a striking discrepancy between the data provided and the labeling, and he or she would not mentally come to the conclusion that these would be enantiomers. The melting point range provided for Example 24 is 194 to 196 degrees, and the melting point range for Example 25 is totally different. It's 168 to 170 degrees. The specific rotations are also not the same. So that the data are very important for a POSITA, and they clearly tell these cannot be enantiomers.

Q. Now, let's take a step back, Dr. Wolf. In Example 25, the chemical structure that is depicted or drawn under Example 25, what is that depicted structure?

A. Just the depicted structure is what we know as of today as tapentadol.

Q. And if that depicted structure under Example 25 is what we know today to be the chemical structure of tapentadol, why would a person of ordinary skill in the art consider the further information provided in Example 25, Dr. Wolf?

A. Well, a person of ordinary skill in the art would never exclude any information that would be provided in the specification, and at the time it was supposedly a new compound. So, one would always be drawn to look at data.

Q. And when you or a person of ordinary skill in the art considers that data, what is the conclusion reached?

A. The conclusion would be that the inventors had not possessed what they claimed to have invented because the melting points are totally off, there could not have been a mental picture even of two enantiomers. So, the conclusion would be, as I say on this slide, that they would not be physically or mentally in possession -- the inventors were not in physical or mental possession of the claimed subject matter.

Q. And you said that would be based on the melting point. Would it also be based on specific optical rotation presented?

A. Correct, the specific rotation is also different.

Q. Thank you, Dr. Wolf. Now, so far in connection with your written description analysis, you have been testifying about the specification of the '593 patent. Did you consider

any further information in connection with that analysis?

A. Yes. I also looked at the prosecution history, as I understand that plaintiffs have brought that up.

Q. And this is demonstrative 22.

A. Yes. Even if I, looking at the prosecution history, I have the same conclusion. The issues that are already discussed remain the same, but it becomes even actually more obscure if one looks at the public record, which is the prosecution history.

Q. Excuse me. This is demonstrative 42. Let's turn to demonstrative 43, Dr. Wolf.

A. Yes, what I'm showing here is, this is from the original '737 patent which was filed in 1995 where Example 25 is referred to as the 1S,2S stereoisomer.

Q. And for the record, this is DTX-950 at page 30, Example 25 in the original '737 parent application. And why would a person of ordinary skill in the art find the 1S,2S disclosure in that application meaningful, Dr. Wolf?

A. It is meaningful because this is clearly not what is in the claims. In the claims we have the 1R,2R stereoisomer. Here we have the 1S,2S.

Q. And let's turn to demonstrative 45, Dr. Wolf. Would a person of ordinary skill in the art in the prosecution history find any further information in connection with the representation in the original parent patent application?

A. Yes, this is a declaration signed by Dr. Buschmann, one of the named inventors, and he signs that he has reviewed and understands the contents of the specification, and he believed everything to be true. That means a POSITA would look at the data and think that those would be objective, true data.

Q. And for the record, this is the July 17, 1995 submission at DTX-1350, page 1.

Let's turn to demonstrative 46 now, Dr. Wolf, moving further in time. Would a person of ordinary skill in the art find any subsequent information meaningful in connection to Example 25?

A. Yes. This is from 1997 where there was a change from 1S,2S to 1R,2S. So, if you look here at Example 25, now the stereo description was changed from 1S,2S to 1R,2S.

Q. And you provided an excerpt here from DTX-952 at page 2 in the middle of demonstrative 46. Why would this be meaningful?

A. Because it was said these were inconsistencies in the R/S stereo descriptions and support for these amendments was found in the original formulas in Examples 24 and 25.

Q. Thank you, Dr. Wolf. Let's explore further the November 1997 submissions in connection with the prosecution history. Let's look at demonstrative 48. Did the applicants present any further submissions in connection with their amendment or Example 25?

A. Yes. What we see here was submitted at pretty much the same time, and from this paragraph, several examples are mentioned, but not Example 25. But if you look at the table that was also part of this declaration, there is an Example 25 which at the time was understood to be the 1R,2S stereoisomer.

Q. And how would a person --

A. There is confusion for a POSITA to even understand what the inventors thought they had invented.

Q. Thank you, Dr. Wolf. Now, as it issued in June 19, 2001, what would a person of ordinary skill in the art have concluded about the disclosure of the '737 patent with respect to Example 25?

A. Again, we see here 1R,2S in the issued '737 patent, and that is not what is in the claims that we are discussing, so the conclusion would have been that they were not in possession of the claim subject matter.

Q. And that was demonstrative 51. Let's turn to demonstrative 52, Dr. Wolf. Now, in connection with the prosecution of the reissue application starting in July 2003, would a person of ordinary skill in the art have found still further information pertinent to what the inventors possessed?

A. Yes. This is from the '593 issue application, and if you can go back to that slide, there is an amendment to correct inadvertent errors.

Q. And what was that amendment, Dr. Wolf?

A. The inventors then changed one more time again the stereo description, and so now it was changed from 1R,2S to 1R,2R.

Q. And did the inventors make any further statements in connection with that amendment, Dr. Wolf?

A. Yes. They said that the compounds in examples which includes Example 25 were incorrectly named.

Q. And for the record, this is demonstrative 54 containing an excerpt from PTX-667 at page 1.

Now, turning to demonstrative 55, Dr. Wolf, in summary, what would a person of ordinary skill in the art, following the prosecution of the '593 patent, conclude about what the inventors possessed?

A. This is a summary of the public record that I just went through where the description was changed from 1S,2S first to 1R,2S, and then finally to 1R,2R. And a POSITA looking at this would be really confused and think that the inventors were confused about what they really possessed.

Q. Dr. Wolf, are you aware that one of the inventors, Dr. Helmut Buschmann, testified at trial in this case?

A. Yes, I am aware of that.

Q. And have you read the trial testimony of Dr. Buschmann?

A. Yes, I did.

Q. Did you review all of Dr. Buschmann's trial testimony?

A. I skimmed over most of that, but I looked at some in

particular.

Q. And did you find any testimony at trial from Dr. Buschmann to be meaningful in connection with your written description analysis?

A. Yes, I think so. I think it's on the next slide, a discussion with regard to the '364 patent, I believe.

MS. SOBOLSKI: Mr. Haw, if we could pull up day 2, please, at page 157 of the trial transcript. And page 157, lines 8 to 15, please. If we could also please pull up DTX-304, which should be the '364 patent. Together, please.

BY MR. SOBOLSKI:

Q. Dr. Wolf, is this the testimony at trial from Dr. Buschmann that you were referring to?

A. Yes, I think it is.

Q. And at page 157, lines 8 to 15 of day 2, Dr. Buschmann was asked about line 46 of the '364 patent, which is DTX-304. And can you please read into the record lines 46 through the remainder of 55 of the '364 patent?

A. U.S. patent numbers '737 and '558 as well as European patent EP 475 B1 disclosed the substance and synthesis of minus 1R,2R, (3-dimethylamino-1-ethyl-2-methylpropyl) phenol hydrochloride in Example 25. As proven by x-ray diffraction the 1R,2R configuration as shown in the drawing of the structure in Example 25 is correct, although the configuration is reported as minus 1R,2S in U.S. patent number '737 and minus

1S,2S in U.S. patent number '558 as well as in EP 475 B1.

Q. And let's take a look at what Dr. Buschmann testified in connection with this portion of the '364 patent.

MR. SOBOLSKI: Mr. Haw, if you could pull up page 159 of Dr. Buschmann's testimony, and if we can cull out, please, lines 13 forward.

BY MR. SOBOLSKI:

Q. Is this the testimony from Dr. Buschmann at this trial that you had in mind, Dr. Wolf?

A. Yes, it is.

Q. And what is meaningful to you about Dr. Buschmann's trial testimony in this case in connection with your written description analysis?

A. I think he -- so, I take his testimony as an acknowledgment that one needs to provide structural data to show the exact and correct stereochemistry of the formula. And so, I believe that Grunenthal actually did that a few years later, so they determined the structure by x-ray crystallography. And so a person of ordinary skill in the art would have expected this to be done in the first place. So, it should have been in the '593 patent. But I agree with Dr. Buschmann that this is a way to do it.

Q. Thank you, Dr. Wolf.

MR. SOBOLSKI: If we can return to the demonstratives, please, Mr. Haw.

BY MR. SOBOLSKI:

Q. Dr. Wolf, let's turn to demonstrative 56 in which you have introduced your analysis of the failure to satisfy the original patent rule of those same claims, 61, 117 and 147. Starting with demonstrative 57, what legal standard were you asked to apply in connection with your original patent rule?

A. It's my understanding that what is playing in the final patent needs to be supported within the specification of the previous patents, and this needs to be a clearly and un -- it needs to be a clear and unequivocal disclosure.

Q. Let's turn to demonstrative 58. In light of the specification of the parent '737 patent, would a person of ordinary skill in the art find that that specification clearly and unequivocally discloses the subject matter of claims 61, 117 and 147?

A. No, because in the '737 patent, what is in Example 25 is the 1R,2S. That's clearly not the 1R,2R which is the stereoisomer in claims 61, 117 and 147. So, a person of ordinary skill in the art looking at this would not find a clear and unequivocal disclosure of the claim subject matter.

Q. Thank you, Dr. Wolf. Let's turn now to demonstrative 59 in which you introduce your opinions related to the non-enablement of claim 8 of the '593 patent.

First, starting with demonstrative 60, what was the legal standard you were asked to apply in connection with your

non-enablement analysis?

A. A person of ordinary skill in the art would have to be able to practice the full scope of the invention without undue experimentation, without excessive work.

Q. And what standard were you asked to apply in connection with whether the nature of the work is excessive or undue?

A. These are actually the factors that I considered for my analysis.

Q. And this is demonstrative 61 listing various factors. Did you consider each of these factors on demonstrative 61 in connection with your non-enablement analysis, Dr. Wolf?

A. Yes, and I have a few slides prepared for this.

Q. Well, let's turn to those, Dr. Wolf. At demonstrative 62, let's begin with how a person of ordinary skill in the art would understand the breadth of claim 8. Did you calculate the breadth of claim 8, Dr. Wolf?

A. Yes, the breadth of claim 8 is very broad.

Q. How did you calculate that breadth of claim 8, Dr. Wolf?

A. I basically looked at the parent structure shown in claim 8, and the first analysis I did is we have two stereo centers in this which gives rise, because of the different spatial orientation of the groups that can be on these stereo centers, to the total of four stereoisomers. And then I looked at what is group X, what can group X be. I show here in the

red block -- excuse me, in the green block. And so this gives rise to another nine possibilities. And then I continue with that analysis. I look at R1, which I have shown here, these are the possibilities for R1, and it gives rise to another 16 possibilities. I then did this for R2 and R3, which adds another multiplier of 71, and then finally R5 and R4 together is another 286. So, all the possible combinations that are covered by this claim are more than 11 million.

Q. For the record, Dr. Wolf has been testifying about demonstrative 62 through 68 about claim 8 of the '593 patent.

Now, let's turn to demonstrative 69, Dr. Wolf. What would a person of ordinary skill in the art conclude in relation to the quantity of experimentation necessary to practice the breadth of claim 8?

A. This is a very large number. It is certainly excessive. So, Dr. Mogil's opinion is one would have to have these compounds in order to test their activity, but I am saying as a chemist, we would have to make them. And this would be a very large number to make.

Q. When you refer to Dr. Mogil's opinion, are you referring to Dr. Mogil's trial testimony in this case in connection with non-enablement of claim 8?

A. Yes.

Q. And what is your understanding of Dr. Mogil's trial testimony in connection with non-enablement, Dr. Wolf?

A. My understanding is that according to Dr. Mogil, one would have to test every individual compound in order to determine its activity.

Q. And what would that in turn entail from the perspective of an organic chemist?

A. Well, as I said, if you want to test those, you've got to make them first, and to make such a large number of compounds would be undue experimentation.

Q. What would the experimentation entail to make those compounds from the perspective of an organic chemist, Dr. Wolf?

A. I did a very conservative analysis of how much work would have to go into making these compounds, and so I came to a conclusion that in the average it would take about two days to make one compound. I kept in mind that one could also run a lot of reactions in parallel to make things faster, but even if one considered -- even if one would say it takes only one day, that would be still an excessive amount of work. In this analysis, I considered the chemistry that was described in the '593 patent, the number of steps, possibility of common precursors, and the reactions that I discussed in the '593.

Q. And that is in connection with synthesizing the 11, over 11 million compounds you've discussed, but did you also consider the salts thereof or the physiologically acceptable acid recited in claim 8 of the '593 patent?

A. Yes, I did. And this is actually the table that I was

referring to earlier from the Berge paper, and so in 19 -- I think this is from 1977, there were 53 pharmaceutical salts known. So, these would be physiologically acceptable salts that are covered by claim 8.

Q. And this is demonstrative 71 containing an excerpt from DTX-176 at page 2. What would a person of ordinary skill in the art understand, Dr. Wolf, about whether there is any additional organic chemistry involved in making these salts thereof?

A. Well, you would have to make them. So, you would have to run the reactions to make these salts.

Q. And turning to demonstrative 72, what would a person of ordinary skill in the art understand about the breadth of claim 8 in light of the further limitation "or salt thereof with a physiologically acceptable acid?"

A. Well, this then would have to be considered, that we would have suddenly 53 pharmaceutically acceptable salts of these more than 11 combination, and that gets us to over 619 million salts.

Q. Let's turn to demonstrative 73. What would a person of ordinary skill in the art conclude with respect to what the specification teaches and the state-of-the-art?

A. So, there is -- in the specification there are 28 examples. That's a relatively small number compared to what we just discussed, millions of covered compounds. And, of course,

a POSITA would understand, chemistry is not predictable, and some synthesis might be complicated, might not work, especially with such a large number of target compounds. So, one would have to remodify chemistry. That would make it even more difficult, more excessive to make these compounds.

Q. Let's turn to demonstrative 74. What would a person of ordinary skill in the art conclude with respect to the relative unpredictability or predictability of the art and the nature of the '593 patent's purported invention?

A. As I already said, chemistry is an empirical art, and it is difficult to make some of these compounds, and chemistry is not predictable. So, some of the precursors might not be available. In my conservative analysis, I actually did not go that far. But some would not be just available. So, you would have to make those, also. There might be problems with stability, unexpected problems, problems with separating enantiomers for sure, and, of course, one would have to not just make them, not just run reaction, but also identify the structure.

Q. Thank you, Dr. Wolf. And finally, what would a person of ordinary skill in the art conclude when in light of the relative skill of that individual?

A. The relative skill of a person of ordinary skill in the art is relatively high and means that a POSITA would insist on developing sound synthetic schemes, determine the identity of

each compound that is potentially made, precursors and the final compounds as well, and so that would require sound empirical data. And then, according to Dr. Mogil, each of these would have to be then tested for an activity.

Q. And is that according to the testimony at this trial that Dr. Mogil gave which you reviewed?

A. Yes, that's necessary according to Dr. Mogil.

MR. SOBOLSKI: Thank you, Dr. Wolf.

THE COURT: Thank you.

Anyone on this side? Do you want to start the cross now? Do you want to take a five-minute break? It's up to you.

MR. GLANDORF: Let's take a five-minute break.

THE COURT: Okay. That sounds fine.

THE DEPUTY COURT CLERK: All rise.

THE COURT: The witness is still sworn in and you are not to talk with counsel regarding your testimony, but you can step down and have the break with everyone else. Thank you.

(Recess at.2:43 p.m.)

(P.M. SESSION)

CROSS EXAMINATION BY MR. GLANDORF:

THE COURT: All right. Let's begin with the cross, please.

Have you exchanged your exhibit binder or no?

MR. GLANDORF: We only have a couple of documents.

THE COURT: Any issue on the documents?

MR. SOBOLSKI: None, your Honor.

Q. Good afternoon, doctor.

A. Good afternoon.

Q. I'm here representing Depomed. My name is David Glandorf.

If we could start with your written description opinion. Could we bring up slide 32 from Dr. Wolf's presentation?

Q. Dr. Wolf, do you recall this slide?

A. Yes, I do.

Q. And these are the three claims that you were challenging as failing under the written description doctrine. Is that right?

A. That's correct.

Q. These are the three asserted species claims. Is that correct?

A. That's correct.

Q. As opposed to the genus claim that's being asserted from this patent, which is the claim 8. Are we on the same page?

A. That's correct.

Q. Now, your written description argument is directed to

the Tapentadol hydrochloride term. Is that correct? And I'll read it out here. It's the 1R 2R 3 3 dimethylamino 1 ethyl 2 methylpropyl phenol hydrochloride.

Is it okay if we refer to the Tapentadol hydrochloride term?

A. That's fair.

Q. Okay. And so your written description challenge to these claims is based on that term. Is that correct?

A. No. I don't think so. My challenge is that a person of ordinary skill in the art looking at the '593 patent would find that discrepancy in the melting points and therefore conclude --

Q. I understand that's your basis. I'm sorry. I have a much more narrow request than that in terms of which part of that claim you are challenging as not being adequately described.

You are focused on the Tapentadol hydrochloride term as opposed to let's say the term "pharmaceutically acceptable salt". Is that fair?

You aren't arguing that there's anything that's inadequate about the description of the words "pharmaceutically acceptable salt". Is that right?

A. You are talking about claim 147?

Q. Yes.

A. Well, my point, I guess, is that if the formula that's

after this phrase starting with minus 1R 2R, it was not possessed by the named inventor and of force the pharmaceutically acceptable salt would not have been possessed either.

Q. That's exactly my question. I just wanted to clarify here though that your focus, the basis, the term that you are saying is not adequately disclosed is the chemical term. And I understand then if that's not there, then you're right, the claim as a whole fails.

But, I just want to make sure you're not saying that there's anything inadequately described by the pharmaceutically acceptable salt on its own.

A. I think that's fair.

Q. And in claim 117, the same thing. Your challenge is to the Tapentadol hydrochloride term, not to anything in the preamble of Claim 8. Let's go to Claim 8. Actually if we could, it's on slide 14.

You haven't offered an opinion today, for example, that there's anything inadequate about the description of treating a mammal suffering from pain. Is that correct?

A. I haven't provided an opinion about the written description of Claim 8 if that is your question.

Q. Okay. That's right. Okay.

A. Well, let's go now to, I understand. I'm sorry. Let me just make sure I clarify. I realize you haven't offered a

written description in challenge to Claim 8. In particular your challenge is claim 117, is that right, under the written description, doctor?

A. Claims 61, 117 and 147.

Q. Focusing on claim 117 again I just want to confirm that you're not offering -- your challenge to the written description there is not based on any of the, what we call here the preamble, the start of a claim up here, the fact that this is a method of treating a mammal for pain.

Is that correct?

A. I think that's correct.

Q. Okay. Thank you. Let's go to your legal slide if we could which I believe is 31. This is your law on written description. And I see your third quote here. Could you read the third quote for us?

A. Sure. "Nor do we set out any bright-line rules governing, for example, the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention, and it changes with progress in a field".

Q. And that's addressing the written description challenge to a genus claim.

But, just so we're clear, you're not offering a written description challenge to the genus claim in this case. Is that right?

A. As I said, it's not about Claim eight.

Q. Okay. Let's go back then. Let's go back to slide 32, Rob. And then could we go alongside it. Put that on the left and put alongside it, slide 15.

You recall testifying about slide 15, Dr. Wolf?

A. Yes, I do.

Q. And you, I believe, told the Court that this is the claim construction that you applied while doing your analysis today?

A. That's correct.

Q. And you applied this term, in fact, during the, for example, during the claims construction. I'm sorry, during the written description challenge. Is that right?

A. Yes.

Q. Okay. And to look, let's look at what we have here. We see the term that's being construed here on the left.

Do you recognize that as the, on the left side of the claim construction, you recognize that as what you and I defined as the Tapentadol hydrochloride term?

A. I think that's correct.

Q. Okay. And so if we go back, your challenge is, for example, of claim 61, the entirety of claim 61 is that term which is being construed by the Court. Isn't that right?

A. I think that's correct.

Q. Okay. And so if we look now back to the claim

construction, could you go ahead and read for us the Court's claim construction of that term, the Court's construction?

A. The chemical compound 1R 2R 3 3 dimethylamino 1 ethyl 2 methylpropyl phenol hydrochloride depicted by the structural formula identified by the number minus 21 in example 25 of the RE '593 patent.

Q. And so the language here is that the Tapentadol hydrochloride term refers to the, what is depicted by the structural formula in example 25. Is that correct?

A. That's correct.

Q. Okay. So, let's go ahead and take that down, Rob. But let's leave 32 up there on the left and then on the right let's go ahead and put slide 33.

Now, here on 33 we have example 25, correct, doctor?

A. Yes.

Q. And, in fact, we have a structural depiction here. Do you see that?

A. Yes.

Q. And so what the Court has decided is that the Tapentadol hydrochloride term refers to the structure as depicted here in example 25. Is that correct?

A. I think that's true.

Q. Okay . And so when you're challenging claim 61 as being inadequately described, a failure of written description, is it your testimony that this structure here is inadequately

described?

A. My testimony is that a person of ordinary skill in the art would look at the whole information that is provided in the specification. And so as a POSITA, one would look into the physical data that clearly don't show possession of the claim subject matter. There is no enantiomeric relationship between 24 and 25.

Q. And I understand that's your testimony and we will unpack that a little bit.

I just want to make sure we're clear here. The meaning of claim 61, according to the Court, is this particular, this single structure here in example 25. Is that correct?

We can go back to the claim construction.

A. Yes, if you can go back to that.

Q. Sure. Let's go back, I think it was 15, Rob, if you want to put slide 15. The Court's construction is that the chemical compound Tapentadol hydrochloride depicted by the structural formula identified by that number minus 21 in the example 25 of the reissue patent, the '593. So let's go back now, Rob, to 33. There is just one structural formula depicted here.

And, doctor, is that correct? And it's identified as minus 21, correct?

A. That's correct.

Q. And so claim 61 refers to a specific chemical structure

depicted here in full.

And is it your testimony today that that structure fails the written description requirement?

A. I haven't testified about just the structure. To me what is important is a person of ordinary skill in the art would look at the whole information and would come to the conclusion that the inventors were not in possession of this example 25.

Q. So, is it your testimony that a person of skill in the art would, when looking at claim 61, for example, would understand it to be that they would need to look at the melting point data and the specific rotation data.

Is that your position?

A. My position is they would look at all the data provided.

Q. And were you involved in the claim construction proceeding in this case?

A. Yes, I was.

Q. And you understand that in this case defendants argued for a claim construction of the Tapentadol hydrochloride term that included the melting point and specific rotation, did they not?

A. I think that's correct.

Q. But the Court ruled in fact that the Tapentadol hydrochloride term refers to this structural depiction. Isn't

that correct?

A. I understand that.

Q. Okay. Now, you would agree that a chemical compound, a structure alone, could satisfy the written description requirement. In general. Not referring to our patent here.

In general is it possible for a chemical structure alone to satisfy the written description requirement?

A. I'm not a lawyer so I don't know what the requirement is.

Q. Well, you testified earlier as to your understanding of what is required under the written description requirement. You don't feel you can answer this question that that structure alone would be sufficient to satisfy the written description requirement?

A. My understanding is that a person of ordinary skill in the art looking into the specification of a patent would have to find evidence that the inventors did invent what they claimed they invented.

So maybe in some cases that could be just a structure. But, I think in this case a person of ordinary skill in the art looking into the specification would see the structure but would see some striking difference between the melting point, between 24 and 25, and the data that are provided clearly tell a POSITA that the inventors were not in possession of example 25.

Q. So, your answer though to the general question, I believe, and you can correct me if I'm wrong, was yes, that in some cases a structural drawing alone would be sufficient to satisfy the written description requirement. Yes?

A. I'm not aware of such a case. What I'm saying is maybe, maybe it could be. I don't think it would work in this case.

Q. Rob, let's go ahead and put up slide 40 if we could. You can take these other two down. So, here we have example 24 and 25.

So just to make our hypothetical a little more exact, if the melting point and optical rotation data was not provided, would you still find a lack of adequate written description here?

A. I think with regard to this patent, yes.

Q. And why is that?

A. So, in this case a person of ordinary skill in the art would still be aware of the prosecution history which shows to a person of skill in the art that the inventors apparently didn't even know what they might have possessed.

Q. Are you referring to there the corrected stereochemistry labels, the ones that the original labels were 1S 2S? Is that what you are referring to?

A. And the fact that there were no agreements with the physical data.

Q. Which physical data?

A. The melting point range and the specific rotations, examples 24 and 25.

Q. You got me there. Let's take the melting point and the optical rotation data out, as well as the specification out of the picture.

Let's ask my question, without that data, would you still hold that these, that the Tapentadol hydrochloride, fails for lack of written description?

A. I think in this case a person of ordinary skill in the art would still see a problem with that. But, there aren't any structural data throughout the '593 patent.

Q. But, I believe you just agreed that we can't have an adequate written description even with the structural drawings alone. Is that right?

A. Again I'm not a lawyer. I think this wouldn't work in this case. I don't know if there are cases where that was --

Q. So, it's the addition here of the melting points of the optical rotational data that for now tips this over to a case where there's no adequate written description. Is that fair?

A. I think I stated that even without those data present, a person of ordinary skill in the art would not conclude that the inventors were in possession of the subject matter.

Q. I see. And is that based on the, again, on the stereochemistry labels?

A. I think that certainly is a strong argument, yes.
Q. And of course when we look at the actual reissue patent, the '593, those stereochemistry labels have been corrected. Is that right?
A. At the end, yes, they have been changed to 1R 2R.
Q. Now, if we look at the two structures drawn here, a person of skill in the art would recognize those as enantiomers, correct?
A. You're just referring to the two pictures, yes.
Q. And if a person of skill in the art were to follow, for example -- you reviewed the whole specification. Is that right?
A. That's correct.
Q. So, if a person of skill in the art was to follow the reaction schemes described that's leading to these two, they would expect those reaction schemes to lead to enantiomers. Isn't that true?
A. I think a person of skill in the art would expect to see structural data for the intermediates that have been formed. This is a reaction scheme that goes through several reactions. As I explained earlier, chemistry is not predictable. And so one would expect structural data for all the intermediates that finally lead to examples 24 and 25. None of that is there.
Q. But, these are routine experiments as of the date of

the patent, as of 1994, isn't that true, these synthetic steps that are described in the examples here?

A. What I explained earlier also with my demonstratives is --

Q. I'm sorry, were you going to answer that question? These are routine steps that are involved in the synthesis leading to example 24?

A. If your question is if these were reactions that were known at the time, then that's correct.

Q. Okay.

A. I would like if I --

Q. Sure. I'm sorry. Go ahead.

A. I would like to add though even with known reactions, as chemistry is not a predictable art, the outcome sometimes is not expected or hypothesized even if it's a known reaction.

Q. And that's exactly my point. I understand that you're right, something could happen and you may not get what was expected as you used the word.

But, just so we're clear, what was expected was the two structures drawn here, correct? That is the expectation?

A. I don't know what the inventors had in terms of expectation.

Q. I'm talking about the steps leading to example 24 and 25 which we just decided were routine. The expectations of the products of those steps are the two enantiomers shown here

in example 24 and 25. Is that true?

A. That could have been the hypothesis but you need to verify those were structural data.

Q. That would be the hypothesis, correct? The person of skill in the art reading those reactions would expect example 24 and 25 to be the rule?

A. There would be a very high chance of other compounds being formed too. So, if you don't have structural elucidation, then you don't know for sure what you have and sometimes the unexpected is happening.

So, if it's a routine reaction that has been known for a long, long time, it's possible and it happens that expected results -- that the results are not as expected. So one would need to get structural data to confirm that, otherwise, you don't know.

Q. Just to be clear, you haven't offered up any side products that someone with skill in the art would end up with instead of these products, correct? You haven't identified any products, side products that someone might get instead of these? A. I haven't run any tests, if that's what you are referring to.

Q. You haven't predicted any products other than what are shown here in example 24 and 25. Is that right?

A. That's correct. I don't think it's necessary because one would know that the unexpected can happen.

Q. And so your testimony is that as of 1994, there was a variety of routine analytical techniques to check to see if your reaction was proceeding as expected. Is that right?

A. That's correct.

Q. And you have a slide, I think, to that. Can we put up slide 34?

These are some of the techniques that a person with skill in the art, in your testimony, would have used in 1994 to see if they were progressing toward the reaction product they expected. Is that fair?

A. These are. I just list here a few possibilities.

Q. There's others as well?

A. One could also think of others.

Q. What about melting point?

A. The melting point does not tell you anything about the structure.

Q. Now, so, if a person of skill in the art in 1994 was given a structure drawn on a paper and asked to synthesize it, first of all, that person of skill in the art could design a synthetic root. Isn't that correct?

A. That's correct. We call it retro synthesis.

Q. Retro synthesis?

A. Yes.

Q. And if they were to check their synthesis, they can check their proposed synthesis, they would perform these

well-known structural data techniques. Is that right?

A. They would verify structures with some of these, typically a combination. But, that depends on what you're making.

Q. So, for example, if they were making a new compound, attempting to achieve a new compound that they had seen drawn on a paper, they could check that with protein or carbon NMR. Is that right?

A. They can apply protein and common NMR spectroscopy to verify the structure.

Q. And possibly something like FD IR as well?

A. That's correct.

Q. And so if a person that's skilled in the art in 1994, for example, had the structure, the Tapentadol hydrochloride, the structure shown on example 25, they would, they could attempt to synthesize that and they would be able to verify that by using the techniques like we have here. Is that right?

A. It's so if you have a retro synthetic analysis and you start with a certain compound to make, for instance, Tapentadol, you could verify those steps through some, using some of the techniques that I have listed here.

Q. Even if you had no reference, even if you had reference to NMR, IR relation to compare it to, you could still use those techniques to determine whether you had successfully prepared

that structure. Isn't that right?

A. You can use the techniques to verify the structure of a new compound so in that case you don't have a reference point.

Q. Thank you.

A. It's fair to say these are well-known techniques at the time.

Q. As of 1994 these are well-known techniques. Is that it?

A. That could have been used but they weren't in the '593 patent.

Q. Let's go to slide 25 if we could. I apologize. Let's try 35.

You testified, for example, about this slide 35 in terms of the importance of structural data. Is that right?

A. That was one of those that I referred to, yes.

Q. But just to be clear, this isn't a guideline for patent drafting, correct?

A. This is a guideline for publication in a journal.

Q. In this specific journal, The Journal of Organic Chemistry. Is that right?

A. This is for The Journal of Organic Chemistry but these are routine techniques. There's nothing stringent about these requirements.

Q. Let's go to the next slide then as well.

And again this guide to materials characterization and

chemical analysis, this isn't written to patent drafters.
Is that correct?
A. No, but I've chosen it because it shows that, it shows that at the time these kind of techniques were used by chemists to identify the structure of new compounds or known compounds.
Q. I understand.
A. But, this is not for a patent. That's correct.
Q. The next slide then I think you have one more in this series. This is a chapter in an undergraduate book. Is that correct?
A. I believe it's from an under grad textbook.
Q. It's written for under grad chemistry students. Is that right?
A. Yes.
Q. Not written for, not directed to patent drafters. Is that right?
A. It's not written for patent drawers. The point is I'm making here is these are basic tests that one would apply to verify the structure of a compound. Even under grads would do that. So, we are not even talking at the level of a POSITA. And one would need to verify the structure of a new compound.
Q. Let's go back to slide 40 if we could. I just want to confirm we had talked about this before. I just want to confirm here you are not challenging that the steps of the patent, you're not challenging that the steps in the patent

would lead to these compounds, right, example 24 and 25?

A. I don't have evidence that they would. What I'm saying is a POSITA would expect structural verification to be convinced that these steps would lead to these structures. Without it, one doesn't know.

Q. You read Dr. Buschmann's testimony, for example, correct?

A. Yes.

Q. And Dr. Buschmann testified that he believed that he had synthesized Tapentadol hydrochloride. Isn't that correct?

A. But, believing is not knowing. We are scientists. We need to know. We might have a hypothesis. We might think it is. But that doesn't mean that's really the compound that we thought we would make.

So, in theory it's possible. But, chemistry is an empirical art. You run the experiment. You must determine the structure of the compound that you thought you might make or might have made. Dr. Buschmann also testified that one can use proof of the structure with crystallography.

Q. Are you aware Dr. Buschmann had performed an NMR to determine whether he had the structure?

A. It's not in the '593 patent.

Q. And you have not, just to be clear, you have not attempted any of the steps that are described in the '593 patent. Is that right?

A. I have not run any of these reactions to make the compound that I described in the '593 patent.

Q. Thank you. Now, you mentioned that it's the addition of a melting point, right, that's part of your basis for claiming that this example 25 fails the written description requirement. Is that right?

A. I think it's fair to say that the large difference in the melting point range that are provided in the patent for example 24 and 25 convinces a POSITA that the inventors did not possess.

Q. Because in your mind it's not possible for those numbers to have been an error. You seem to have eliminated that possibility.

Is it possible that these melting points here could have been an error?

A. So, in general there can be an error if you determine melting points. That's well-known in the art. It was well-known as of the '90s as well.

Q. You said there cannot, I'm sorry, you said cannot be an error in the melting point?

A. There can be error.

Q. There can be.

A. Like with every experiment you are running, you can have an error.

Q. And you understand Dr. Buschmann's testimony to be that

this was an error. This was a listing error here in example 25. You saw that testimony in Court, correct?

A. I think what he said I think that's not convincing to a POSITA that this was an error.

Q. And why is that?

A. I think if I can I would have two things to say to that regard. The first thing is, as I said earlier, a POSITA would look at everything that's in the specification. And so we see here, as I said earlier today, that the enantiomer minus 21 is related to example 24 which is the purported enantiomer plus 21.

Q. Those are enantiomers, that's right?

A. That remains to be discussed. But, this is information that a POSITA sees. So a POSITA would look, for instance, at more information. And so if you look in the '593 patent, there's a description of how these were made. And this is what this is referring to. At the very end the material supposed to go through two purification steps, if I remember that off the top of my head correctly. One is an extraction and one is a crystallization.

These are, as I mentioned earlier, what once you run a reaction, you purify the compound before you determine the structure.

So, a POSITA would look at this and see that these two examples would have been through the same double purification

processes. They should have the same purity. They should have the same purity profile. They should have the same melting points.

So, that is certainly striking. The difference in the melting points is absolutely striking. These cannot be enantiomers.

If I may, my second point is, if you just assume that a POSITA, if you just assume for a moment that they had considered that they could be enantiomers, which I don't think they did, it's even an under grad would realize they cannot be enantiomers. The melting points are totally off.

So, if you look at this and you say the melting points are totally different, you just take five minutes to get to double check the melting point or you do some structure elucidation then you know it's really screaming at a POSITA and an under grad student that the melting points are absolutely off. They are not even close. These cannot be enantiomers.

Q. I think we are on the same page here, doctor. I think you've talked now you gave two examples, walked through two reasons why these were these melting points. But, both your reasons were they should be the same. They should be the same because they are enantiomers.

What I'm asking is isn't one explanation then that this is an error, it's a listing error or a measure error, either one, but it's an error. This melting point is simply an error.

And in fact isn't that what Dr. Buschmann testified?

A. A person of ordinary skill in the art would not see that in the specification. So, a person of ordinary skill in the art would look at what's provided in the specification and it's hypothetical what the reason is.

But, a person of ordinary skill in the art would expect that the inventors, if they had thought even of these being enantiomers, would have seen that right away. As I said, it's screaming. Even an under grad, not even a POSITA, knows they cannot be enantiomers. So, you wouldn't provide this data and throughout the whole prosecution history.

Q. They could be enantiomers or they could be an error. Is that fair?

A. I think that's hypothetical. I think that could be just the melting points of what --

Q. It could be the melting point. It could also be an error. Are you disagreeing with that?

A. I think in theory. But, practically speaking, I don't think that's convincing to a POSITA looking into the specification.

Q. And you talked about the whole specification. Let's talk about the specification as a whole here.

We have two structures shown, correct?

A. That's correct.

Q. Those structures are enantiomers as shown, correct?

A. Just the structures alone.

Q. And we talked about the reaction scheme. We mentioned the reaction schemes are routine steps and that these are the expected results, correct?

A. As I said --

Q. I understand it's not guaranteed, but the expected results are that it would react, it would result in the enantiomers listed here, correct?

A. I don't know what the expected results were.

Q. You can't follow those synthetic reactions and see what the expected results are?

A. I don't know what the inventors had in their minds. That's not in the specification. I can see that the steps that were applied could make this possibly in theory. But, one would have to test it and it would be just using one of the techniques that we've discussed to verify the structure.

It's not therefore the final product. It's not even therefore the precursors.

Q. Let's go ahead and look at '593. Let's go to example two on column seven. Let's go to 668. I think we have a better copy. Do you have that there?

A. This is in the handouts.

Q. Yes, it's in one of the two handouts.

A. All right.

MR. SOBOLSKI: Your Honor, just to clarify the

record, PTX 668 is not the '593 patent, it's the '737 patent.

MR. GLANDORF: So we are switching now to the 312. We are going to 668 which is the original.

Q. Do you have example two, doctor.

A. I'm there.

Q. Could you explain what is happening in example two here?

A. So, at example two it says enantiomers of 1-2S 3S 1 dimethylamino methyl 1-3-methyoxphenyl cyclohexanol hydrochloric plus 1.

Q. So you've reviewed these steps previously?

A. I have looked at the reaction awhile ago, yes.

Q. Can you explain at a high level what's happening in example two?

A. So, what happened here with compounds, compound one was that the base was released with basically an extraction procedure. And the resume was then separated on the chiral edge POC column. So that is a procedure to separate enantiomers.

Q. And the enantiomers that had been separated, how are they designated? Not their chemical names.

A. That would be the minus one and the plus one.

Q. Okay. So, now if we go ahead to example 25, so the example 25 is using the minus one enantiomers from example two. Is that right?

A. That's correct.

Q. Taking then the minus one enantiomer, what it says is you use the minus one enantiomer from example two and then you put it through the reactions that are listed in example 24. Is that right?

A. That's correct.

Q. Okay. And again I'm asking you, a synthetic chemist, if you were to put it through the reactions in example 24, if you start with minus one, put it through the reactions of 24, the expectation is, you are going to say we have to prove it, I know. But, the expectation would be to achieve the structure shown here in example 25.

Isn't that correct?

A. So, that can't be the expectation that putting these enantiomers through the several reactions, we skipped over a few, that in theory they could make the examples 25 or 24.

Q. In theory they would make that, correct? In theory?

A. They could.

Q. They could. You wouldn't say that they would?

A. Well, so, in theory if everything goes as expected, if you start with enantiomeric study materials, so that you can make enantiomeric products, that is the theory. The melting points show us that this apparently didn't happen.

Q. But, just so we're clear, the reaction scheme is consistent with the structural drawing, correct?

A. I would say it's fair to say that one would have to have structural data to say the drawing is right.

Q. All right. Let's talk a little bit but utility. Maybe we can come back to this example here in a minute. Let's go to slide 20 from Dr. Wolf's presentation.

Now, you talked about some of the utility shown here for some of the compounds. Do you recall that?

A. Yes, I do.

Q. And each and every compound in this example shows analgesic activity. Is that correct?

A. Based on Dr. Mogil's opinion, I don't think that this table shows any analgesic activity.

Q. You have your own opinion whether there's analgesic activity here?

A. I am relying on Dr. Mogil's opinion.

Q. You have no opinion of your own on that point apart from Dr. Mogil?

A. I have looked at that table and I can tell you from the perspective of an organic chemist there is a lot missing that makes me, that's not convincing me that these are adequate data that show analgesic activity.

Q. Now, a person of skill in the art would expect that a new compound that is structurally similar to a known compound with an established utility and expect that the new structurally similar compound would also have that utility,

correct?

A. I don't think so. I think that there could be the hope it does.

Q. That would be the expectation, correct?

A. As I explained earlier with the example of the Thalidomide, that could certainly not be the expectation.

Q. I understand that it may not be reality. But, the expectation would be that a new compound that is structurally similar to an existing compound with utility would also have that utility, right?

A. I think one would have to get the data to prove it.

Q. Let's look at your deposition testimony if we could. If we could pull up his deposition testimony. This is the 2015 deposition. Let's go to Page 173-23 and we are going to continue to the next Page 174-12.

Q. Now, at your deposition, Dr. Wolf, you were asked how did you or what did you mean by structurally similar in the context of this assertion. And I'm going to go ahead and read your answer here.

You said, So, in some cases we know that a class of compounds generally has a certain activity, for example, biological activity. And in some cases there is a good understanding of the structure activity relationships.

So it's a reasonable expectation that a small change in the structure of a proven biologically active compound will

yield another biologically active compound. It may not be clear if that will be a better or not so effective compound. But, there's a reasonable expectation that it will have biological activity.

THE COURT: You're standing. I think we have an issue.

MR. SOBOLSKI: We would ask that the previous question be read because this clearly refers to a designation which begins at Page 173, Line 12. In fact, this is a question about something that was in Dr. Wolf's reports.

THE COURT: Go ahead.

MR. GLANDORF: I would suggest if Counsel wants to explore that, he can do that.

THE COURT: I think that's apt. That sounds fine. Thank you.

Q. Did I read your answer correctly here, Dr. Wolf?

A. I think that's, yeah, you read this correctly.

Q. And so there can be a reasonable expectation for a structurally similar compound that if one has a certain biological activity, the structurally similar compound would have that activity as well. Is that right?

A. So, if you have a good understanding of structure activity relationship that can certainly guide a POSITA and suggest some structural modifications with an expectation that one could potentially even make a better drug.

Q. Let's go to slide 63 then which is to be Claim eight.

You would agree, Dr. Wolf, that there is a structural similarity here among the compounds covered by Claim eight, correct?

A. Could you be more specific? There are so many compounds claimed here. Indeed the functional groups that are here are not necessarily similar. One has to define what is similar.

Q. Well, we can get to that. I think we'll dig into that. Let's start at the highest level.

This is the backbone of the molecule here, correct?

A. That's correct.

Q. R1 and referring to the substituent that can be placed on the backbone, correct?

A. That's correct.

Q. So, this is a structural similarity here. We can talk about the extent of it. But, let's start at the beginning. There is a structural similarity here, correct?

A. Not to the extent that all these compounds that are encompassed by Claim eight would necessarily be considered structurally similar.

Q. So you're not even willing to say there is some level of structural similarity here?

A. Well, some might be very similar but some might not be similar at all.

Q. Your testimony is there is not a level of structural similarity that goes across this entire genus. You have a backbone there. I think, as you said, that's common.

So, the question here is is there a sufficient structural similarity in this class such that a person of skill in the art would expect that if utility was shown for some compounds, it could be expected of other compounds?

A. I haven't opined on that. But, I think I wouldn't say that.

Q. I'm sorry, you haven't opined on that but you wouldn't say that?

A. Do you mind asking your question again?

Q. Yes. Is there a sufficient structural similarity among the compounds in this class so that if some were shown to have certain biological activity, you would expect others in the class to have that activity?

And your answer was that you haven't opined on that, correct?

A. So, what I'm saying is out of millions of compounds there could be, you expect that you might find one or some that have activity in the table to begin with. My understanding is activity isn't even shown.

Q. And I understand that. And that's a separate question.

My question is if activity is shown to some of the compounds, is there sufficient structural similarity here that

you can then expect others in this class will also have a similar activity?

A. I don't know of structure activity relationships that have been developed for these that I could show you. If you gave me one compound that has analgesic activity that I could tell you and a specific other one that would also have that activity.

As I said earlier, even if you look at mirror images that look so much alike, it's known some have activity in a certain way and others don't.

Q. My question, doctor, is have you analyzed, have you analyzed the genus here to see if there is a structural similarity to the extent that you could apply, that you would have expectation of biological activity if some were shown to be active.

Have you done that analysis? Have you presented an analysis as to the degree of structural similarity here?

A. I don't think I have.

Q. You rely on Dr. Mogil for the idea that each and every compound needs to be tested. Is that right?

A. I think that's correct.

Q. And let's, we can come to the salts in a minute. But, in terms of actual compounds, you listed the number as 11 million. Is that right?

A. Whatever I had on my demonstratives.

Q. I believe it was 11 million.

A. Yes.

Q. So, you haven't offered an analysis, for example, of what percentage of that category would have to be tested for utility before you could have an expectation across the genus. Is that right?

A. My understanding is you would have to test each orb.

Q. You would have to test each orb. If you tested the first ten million you would have to test the last million. Is that right? That's your opinion?

A. So I'm relying my opinion on what Dr. Mogil has opined and that is you have to test each one to know if that particular compound has that particular activity.

Q. You wouldn't be able to say, if you tested a thousand, that that would provide an expectation across the class? You are relying on Dr. Mogil. Is that right?

A. I think if you have tested a thousand and if these have proven biological activity, that might give you an actual understanding of structural relationships. And then you might have a way to expect that certain structures that are covered by Claim 8 might also have that activity.

Q. And in your opinion must utility be shown by a scientifically rigorous method?

A. Again I'm not a lawyer. But, as a scientist, I would expect that a rigorous method would be applied to show the

utility.

Q. Well, as you applied your opinion here today, does your opinion call for each -- require that each compound be examined for utility by scientifically rigorous method?

A. That's my understanding of what Dr. Mogil opined.

Q. Is it your understanding in offering this opinion today that each compound must be shown to be advantageous over Tramadol?

A. I haven't opined about that.

Q. You did talk about the time it takes to make all the compounds. Do you recall that?

A. That's correct.

Q. And in your opinion it would take roughly two days for a compound. Is that your opinion?

A. That's what I've said, yes.

Q. And you are not arguing that taking two days to prepare a compound could be undue experimentation?

A. That's an average for other compounds that would have been required.

Q. I understand. But if we were looking at one compound and it took roughly two days, you wouldn't argue that that's undo experimentation, correct?

A. For one particular, for one, just one compound, no.

Q. Let's look at slide seven here, Rob, if we could. Actually let's go, Rob, to 74.

You mentioned some potential problems here with producing these compounds. Is that what's shown here on slide 74?

A. Yes, that's correct.

Q. But, you haven't identified a problem with any particular compound in Claim eight? You haven't identified any particular precursor that would be missing, have you?

A. I have not done that. But, my understanding is that based on the large number of compounds that are covered by Claim eight, you would certainly run into these issues.

Q. But you haven't identified any final compound, for example, that might have a lack of stability, have you?

A. No, I have not identified those details.

Q. You haven't identified any particular compound that is likely to be difficult to manufacture, to synthesize, correct, no particular compound?

A. I haven't provided that information.

Q. And if a person of skill in the art tried a synthetic path and reached a dead end, they would find a way to redesign that synthesis, correct?

A. That's not necessarily the case. But, that person would make a try.

Q. Let's look at your deposition testimony. Rob, same deposition. Go to 159-11 to 160-10. So you are being asked here a priori is also known which if any synthesis of compounds

covered by asserted genus claims, a person of ordinary skill would have been expected to fail due to lack of facility. A priori is it also unknown.

You asked to repeat the question. Read back. You said, This chemistry is not fully predictable so one would have to find out by experiment.

The next question was, Now, you'd agree in 1994, you would agree in 1994 a person of ordinary skill would have been able to revise a synthetic round that it is a dead end for one of the claimed compounds of the asserted genus claims without undue experimentation.

And your answer was, I think a person of ordinary skill in the art as of 1994 would be able to realize that he or she hit a dead end and would then come up with another retro synthetic scheme or at least route to the product that could include the development of reactions that were not known at the time.

Did I read that correctly?

A. I think so. So, one would try to come up with another idea of making the compound. If that would be successful again one would have to, of course, determine by the experiment structural elucidation.

Q. Let's go back to, I think it's slide 60. How about slide 14.

And so the structure shown here in Claim eight, these

could be prepared with relatively routine synthetic routes known to a person of skill at the time with some reasonable expectation of success, correct?

A. This encompasses a very large number of structures. And because of that, I would not think it would be a reasonable expectation of success that all of these would be successfully synthesized.

Q. But if we were to pick just any one particular compound, you haven't identified any compound for which there would not be a reasonable expectation of success in this genus, correct?

A. I haven't identified any particular but I think it would be clear to a POSITA that out of so many and with some of the groups attached to this backbone, there would be complications. And there would be compounds very difficult to be made and some probably would not be made.

Q. And that's your general statement. But, again, you haven't identified any particular group or compound in your opinion that you presented today that would be difficult to make. Is that right?

A. I have not shown any particular structure, yes.

Q. Okay.

Let's go to slide 58, if we could. Let's put back up our claims construction slide next to it. That's 15.

Now, I believe your testimony on the original patent

rule was that any claim in the reissue needed to be disclosed in the original application. Is that correct? Is that a fair statement of the standards?

A. I think that's correct.

Q. If we look at claim 61, for example, the question is is this disclosed in the original patent. Is that right?

A. That's correct.

Q. And again if we look at the claim construction, we see that the entire claim here is construed by the Court to refer to this structure here in example 25. Is that right?

A. I understand that claim construction.

Q. And this structure shown here in example 25, that structure, this structure was shown in the original patent, correct?

A. That is correct together with the melting points.

Q. Okay. Again, the claim construction doesn't refer to the melting point?

A. But, this is something that a POSITA would certainly see in the specification. And so it shows the POSITA that there cannot be an enantiomeric relationship.

Q. In your reading of it when a POSITA reads this claim, they would include the melting point in that understanding. Is that your testimony?

A. I don't think that's my understanding of the claim construction that we have, no. But, I'm saying that a POSITA

would understand that claim construction and look what's in the specification and there is that claim construction. And then there is this vast discrepancy between the melting points between example 24 and 25.

Q. Okay. And if we look here at claim 117 again it has that Tapentadol hydrochloride term. And you understand that, according to the Court, to be a reference to this structure that was in the original patent. Is that right?

A. Yes, I think we are looking at the same claim construction.

Q. And if we look at claim 147 again, it has that same Tapentadol hydrochloride term. And it's referring to, according to the Court, again, the structure that has been there since the original patent, correct?

A. Claim 147 actually is not having the hydrochloride term in it.

Q. I see. So it's referring, is it fair, though, to understand that to be referring to the structure depicted here minus the hydrochloride?

A. And then plus a pharmaceutical salt.

Q. Plus other salts as well. Okay. I understand that.

Now, you testified that this entry in the World Health Organization drug information would make Tapentadol hydrochloride obvious. Is that correct?

A. That's correct.

Q. Because what's shown here on this page, the name and the structure, is enough to disclose to a person in the art and to give them an understanding of what Tapentadol hydrochloride is. Is that right?

A. Yes. We have a name and a structure and that's referred to as Tapentadol.

Q. And so your opinion here, if we, let's go back a slide here, let's go back one more. So your standard here on obviousness, I'm sorry, your opinion here on obviousness is based on the patent has a priority date in 2005. Is that correct?

A. That's correct.

Q. And did you do an analysis to determine that the priority date should be 2005?

A. I was basically working with Dr. Mogil's opinion that this would be the earliest time that utility could have shown.

Q. Dr. Mogil provided you with that, with the standard? It was Dr. Mogil's opinion that the priority date should be 2005?

A. I think that's true.

Q. You didn't do an analysis to determine that the date should be 2005, correct?

A. I've worked with his analysis of that priority date.

Q. And so your opinions on obviousness here in this section, those are only relevant if there is a priority date of

2005, correct?

A. I think it's fair to say that the World Health Organization document is from 2002. So it probably would be effective earlier than 2005.

Q. Let's ask it this way, if the Court decided that a priority date of 1994 is appropriate for this patent, your obviousness opinion is irrelevant, correct?

A. I think my obviousness opinion is only for the later time.

Q. And again if the Court grants a priority date or determined that a priority date of 1998 should apply, again your obviousness opinion is not relevant. Is that right?

A. I think that's true.

Q. And so let's go forward a couple of slides back to our W.H.O. document here.

Just so I understand, it is true that this structure shown here is Tapentadol hydrochloride. Is that right?

A. That is the structure of Tapentadol.

Q. That is the structure of Tapentadol. If it was associated with the hydrochloride, it would be Tapentadol hydrochloride?

A. That's correct.

Q. And this is the same structure again minus the hydrochloride that's shown in example 25 of the patent?

A. Just the structure alone?

Q. Yes.

A. I think they are the same.

MR. GLANDORF: Can I confer with my colleagues for a moment?

THE COURT: Yes.

(Off the record discussion).

MR. GLANDORF: No further questions.

THE COURT: All right. Thank you. Counsel.

MR. SOBOLSKI: Briefly, your Honor.

THE COURT: Redirect. Yes, please go ahead

REDIRECT EXAMINATION BY MR. SOBOLSKI:

Q. Mr. Haw, if I can ask you to please recreate the split between Dr. Wolf's demonstratives 15 and 33.

Dr. Wolf, do you recall what Counsel for Depomed put up, this split screen with your demonstrative 15 and your demonstrative 33?

A. I think so.

Q. And on the left side of the demonstrative 15 that presents the claim construction that the Court has issued in this case in connection with a term that appears in claim 61, 117 and you read that into the record.

Do you recall that?

A. Yes, I do.

Q. Mr. Haw, if I can ask you to emphasize under the chemical compound, please.

Now, Dr. Wolf, in light of this claim construction and the information about which you testified earlier this afternoon, is it your opinion, is it your testimony that a person of ordinary skill in the art would conclude that the inventors possessed the chemical compound minus 1R 2R 3 3 dimethylamino 1 ethyl 2 methylpropyl phenol hydrochloride depicted by the structural formula identified by the number minus 21 in example 25 of the RE '593 patent?

A. No, as I said earlier, a POSITA would not conclude that they possessed this.

Q. Thank you, Dr. Wolf.

You can take that down, Mr. Haw. And if you please put up Page 173 of Dr. Wolf's November 2015 deposition transcript.

Dr. Wolf, do you recall when Counsel for Depomed asked you some questions about your deposition testimony on Page 173 here?

A. Yes, I do.

Q. Mr. Haw, can we please call out lines 12 through 25.

And do you recall that Counsel for Depomed asked you about a question below the question that appears here at 12, Dr. Wolf, at Line 12?

A. I think that's true.

Q. I am going to ask you please for the record to read the question you were asked preceding that question. Please read, for the record, the question that you were asked at Page 173

starting at Line 12. And please also read your answer at line 22 into the record.

A. Okay. Now going back to your opening report at Paragraph 88, the sentence following what we've looked at before starts at the top of Page 29, "a POSITA might reasonably expect that a supposedly new compound that is structurally similar to a known compound with established utility might also have that utility. But, a POSITA would require empirical demonstration of that assertion on a compound by compound basis".

Q. Do you see that?

A. Yes.

MR. SOBOLSKI: No further questions, your Honor.

THE COURT: Thank you very much. Anything further?

MR. GLANDORF: One moment.

THE COURT: Yes, take a few minutes.

MR. GLANDORF: No further questions.

THE COURT: All right. Thank you very much. We are concluded with this witness. Thank you very much.

THE WITNESS: Thank you, your Honor.

THE COURT: You may step down. You are released now. Your testimony is concluded. We appreciate your time with us today. Thank you so much.

THE COURT: Counsel, is there anything else for

today?

MR. SCHULER: That's it for today. We advised, I think we presented the Court with the proposed schedule for Monday.

THE COURT: Which sounds fine. As I indicated, if there is any wrinkle with respect to the weather, we will get in touch with you. Can we confirm, we have no testimony tomorrow, correct?

MR. SCHULER: Correct.

THE COURT: Just so we don't have stray folks coming in, we will say it again.

What time are you folks thinking for Monday? Is nine good?

MR.FITZPATRICK: Yes.

MR. GLANDORF: Your Honor, I have one matter. I have a list of exhibits from just a couple of --

THE COURT: Are you going to be handing them in?

MR. GLANDORF: We conferred and I believe we have agreement.

THE COURT: Are you going to be exchanging them?

MR. GLANDORF: It's testimony from Dr. Buschmann and Dr. Gruss.

THE COURT: How should we handle it? We can have it read into the record.

MR. SCHULER: It's long.

THE COURT: How many exhibits?

MR. GLANDORF: We have 68.

MR. FITZPATRICK: We can just put it on the docket, your Honor.

THE COURT: We need a copy so we can keep track of it.

MR. FITZPATRICK: Can we just put the document on the docket?

THE COURT: Yes, let's do that. I know we will be adding to it. We're just at a point where you've got up a little bit.

Any other issues before we disband?

MR. SITZMAN: One quick thing. I just want to get one quick item, your Honor. Your Honor, we've got one small item.

THE COURT: Okay.

MR. SITZMAN: And it's not in evidence, but, it's in your book. And it's a demonstrative from Dr. Martin and it's slide 54. We'd like to remove that from everybody's books since there was no testimony on that. And there's not going to be any evidence offered on the information that's contained in that page.

THE COURT: Okay. So, do you want mine back or do you want to just give me the additional one and I will swap it out?

MR. SITZMAN: We can just rip it out.

MR. FITZPATRICK: Just take the page out. Actavis has no objection, your Honor.

THE COURT: Okay. Good.

MR. FITZPATRICK: Just to clarify for the record, your Honor, it's Number 54.

THE COURT: Hold on one second.

Any additional business before we conclude for the day and the weekend? Anything else? Last chance. All right. Thank you everyone. Have a good weekend. I will see you on Monday. Take care. Thank you.

(Whereupon the matter was concluded)